"TO ESTIMATE THE PREVALENCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE"

Dissertation submitted to The Tamil Nadu Dr.M.G.R. Medical University in partial fulfilment of the requirements for the degree of

Doctor of Medicine (M.D) in

Tuberculosis and Respiratory Diseases

Branch – XVII

Institute of Thoracic Medicine,

Madras Medical College &

Rajiv Gandhi Government General Hospital

The Tamil Nadu Dr. M.G.R. Medical University

Chennai – 600032

Tamil Nadu

India

May 2019

BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"TO ESTIMATE THE PREVALENCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE "** is the bonafide work done by **Dr.V.ARUNSHANKAR** during his **M.D (Tuberculosis and Respiratory Diseases)** course in the academic years 2016-2019, at the Institute of Thoracic Medicine and Rajiv Gandhi Government General Hospital – Madras Medical College, Chennai. This work has not previously formed the basis for the award of any degree.

Prof. Dr. A.MAHILMARAN M.D., D.T.C.D
Director, Institute of Thoracic Medicine,
Professor and Head, Department of Thoracic Medicine,
Rajiv Gandhi Government General Hospital and Madras Medical College,
Chennai.

Prof. Dr.R.JAYANTHI M.D., FRCP(Glasg),
The Dean,
Rajiv Gandhi Government General Hospital and Madras Medical College,
Chennai.

DECLARATION BY THE GUIDE

This is to certify that the dissertation titled **"TO ESTIMATE THE PREVALENCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE"** is the Bonafide work done by **Dr.V.ARUNSHANKAR** during his **M.D (Tuberculosis and Respiratory Diseases)** course in the academic years 2016-2019, at the Institute of Thoracic Medicine and Rajiv Gandhi Government General Hospital – Madras Medical College, Chennai, **under my guidance**.

Signature of the Guide,
Name and Designation of the Guide:
Prof. Dr.A.MAHILMARAN .,M.D., D.T.C.D.,
Director, Institute of Thoracic Medicine,
Professor and Head, Department of Thoracic Medicine,
Rajiv Gandhi Government General Hospital and Madras Medical College,
Chennai.

MADRAS MEDICAL COLLEGE & RAJIV GANDHI GOVERNMENT

GENERAL HOSPITAL, CHENNAI – 600 003

DECLARATION BY THE SCHOLAR

I hereby declare that the dissertation titled **"TO ESTIMATE THE PREVALENCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE"** submitted for the degree of **Doctor of Medicine (M.D) in Tuberculosis and Respiratory Diseases, Branch XVII** is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or other similar titles.

Place : Chennai [DR.V.ARUNSHANKAR]

Date : Signature of the scholar

ACKNOWLEDGEMENT

My sincere thanks to **Prof. Dr.R.JAYANTHI M.D.,FRCP(Glasg), The Dean**, Rajiv Gandhi Government General Hospital and Madras Medical College for allowing me to do this dissertation and utilize the Institutional facilities.

I am gratefully indebted & whole heartedly conveying my gratitude to Director, Institute of Thoracic Medicine., Professor and Head, Department of Thoracic Medicine, Rajiv Gandhi Government General Hospital and Madras Medical College **Prof. Dr. A. Mahilmaran, M.D., D.T.C.D.,** for his invaluable guidance, advice and encouragement throughout the study.

I sincerely thank **Prof.Dr.O.R.Krishnarajasekhar, M.D.,D.T.C.D.,** Professor, Department of Thoracic Medicine, Rajiv Gandhi Government General Hospital and Madras Medical College, for sparing his precious time in guiding my dissertation writing and reviewing it.

My sincere thanks to **Dr.A.Sundararajaperumal, M.D.,D.C.H.,** Associate Professor, Department of Thoracic Medicine, Rajiv Gandhi Government General Hospital and Madras Medical College for his guidance and reviewing the thesis.

I am bound by ties of gratitude to Assistant Professors **Dr.V.Sundar, Dr.G.S.Vijayachandar, Dr.K.Veena, Dr.T.Ranga Rajan, Dr.P.Arul Kumaran, Dr.DeepaSelvi, Dr.N.Murugan, Dr.Sasikala, Dr.Anbarasi, Dr.Ammaiyappan, Dr.Arun Babu, Dr.C.palaniyappan,Dr.Rajeswari and Dr.Poonguzhali.**

I would like to thank my seniors especially **Dr.P.P.Ramkumar** and **Dr.S.Sivakumar** for guiding me in doing my thesis. I would like to thank my batchmates and all my juniors for rendering their help whenever I have asked for, in completing my dissertation.

Last but not the least, I am profoundly grateful to all the patients, who were subjects of my study for their participation and co-operation.

CONTENTS

INTRODUCTION

INTRODUCTION

Chronic Obstructive Pulmonary Disease is a common, preventable and treatable disease characterized by a persistent respiratory symptoms and airflow limitation due to airway and / or alveolar abnormalities usually caused by a significant exposure to noxious particles or gases.

COPD represents an important public health problem and is a major cause of chronic morbidity and mortality throughout the world. COPD is currently the fourth leading cause of death worldwide [1] but it is projected to cause over 6 million deaths by 2020 and thereby becoming a third leading cause of death in the world.

The Global Burden Of Disease study found that COPD is a major contributor to disability and mortality in the world. In 2005 COPD was the 8th leading cause 0f Disability Adjusted Life Year lost, but by 2013 COPD was ranked at fifth leading cause of Disability Adjusted Life Year lost.

COPD patients frequently have associated cardiovascular disease, skeletal muscle dysfunction, lung cancer, metabolic syndrome, osteoporosis , depression and anxiety. These comorbidities can independently influence the mortality and hospitalizations in COPD patients.

RISK FACTORS OF COPD:

COPD results from a complex interaction between genes and environment. Though cigarette smoking is the commonest risk factor, there are evidences that non-smokers may also develop COPD.

Exposure to Particles:

Cigarette smoking is the commonest risk factor for COPD. Other types of tobacco such as pipe, cigar [2] are also risk factors of COPD. Passive exposure to cigarette smoke is also known an Environmental Tobacco Smoke (ETS), is also a known risk factor for COPD. Occupational exposure, indoor and outdoor air pollution are other risk factors of COPD.

A Swedish cohort study [3] reported that population attributable risk for development of COPD in smokers is 76.2% . In India most of the smokers are using bidi for smoking than cigarette [4]. Ventilatory function deterioration is common among smokers than non-smokers.

In males, the average decline in FEV1 is around 9 ml per year for each pack-year of smoking. In females the average decline in FEV1 is approximately around 6 ml per year for each pack-year of smoking. Eventhough tobacco content is low in bidi, bidi smokers are more vulnerable to develop COPD than cigarette smokers [5].

Risk of COPD is proportional to the number of cigarettes or bidis smoked per day. Risk also increases with the duration of smoking. The risks are lower at a lower dose and lesser duration of smoking .The Lung Health Study, stated that there is an accelerated decline in FEV1 in COPD patients if they continue smoking.

Chronic inhalation of particles and the gases carry a greater risk for developing COPD. But we are not able to estimate the correct prevalence of COPD among workers because most of the workers are also smokers and those with COPD drop out from work. The American Thoracic Society states that 15% of COPD cases are due to occupational exposure.

People working in rubber industry, plastic industry and leather industry are at increased risk of COPD[6] Also, people who work in textile mills and food product manufacturing unit are also at increased risk[7].

In developing countries like India, especially in an urban population, outdoor air pollution has been implicated as a cause for COPD and various other respiratory diseases [8]. It is due to the pollutants from industries and motor vehicles causing pathological changes in the lung and airway. A prior study observed that higher traffic density is associated with increased risk of COPD in women population. These pollutants are known to cause bronchial hyperactivity, airway oxidative stress, pulmonary and systemic inflammation [9].

Biomass fuel is obtained from the combustion of wood, dried dung, and crop residue. Exposure to biomass fuel is an important source of indoor air pollution. It is an important cause of COPD among the women population, especially in rural India. Combustion of biomass fuel especially in closed spaces results in the inhalation of the toxic gases which contributes to the development of COPD. The risk of COPD among women in urban population is less when compared to women in rural areas. This is because women in rural areas frequently use biomass fuel whereas women in urban areas use LPG as fuel for cooking purposes.

Genetic factors:

The genetic factor that is documented is a hereditary deficiency of alpha 1 antitrypsin (AATD) [10], a major inhibitor of serine proteases. It illustrates the interaction between the gene and the environmental exposures that predispose an individual to Chronic Obstructive Pulmonary Disease.

Gene encoding for the matrix metalloproteinase 12 (MMP12) was related to decline in lung function.

AATD accounts for approximately 1-2% of total cases of COPD.

Conditions suggesting alpha 1 anti-trypsin deficiency are:

- Early onset emphysema (age less than 45 years).
- Emphysema in a non-smoker.
- Emphysema predominantly in lung bases.

- Family history of early onset emphysema or non-smoking related emphysema.
- Bronchiectasis without any other aetiology[2]

AGE AND GENDER:

Age is often listed as a risk factor for development of COPD. Aging of the airway and lung parenchyma may resemble some of the changes associated with COPD.

In earlier days, COPD prevalence and mortality were greater in men, but recent data from developed countries has reported that the prevalence of COPD is almost equal among both the sexes, this could be due to changing trends in tobacco smoking.

Childhood lower respiratory tract infection:

Ventilatory function in an adult depends upon the lung function in their childhood. Hence, the respiratory tract infections that occurred during childhood can affect the lung development and tend to increase the risk of developing COPD later [11].

Airway Hyperresponsiveness:

In COPD, airway hyper-responsiveness is often associated with an accelerated decline in FEV1.However airway hyper-responsiveness does not predict bronchodilator responsiveness.

Socioeconomic status:

Lower socioeconomic status is one of the factor associated with increased risk of COPD. This is because, an increased amount of smoking is seen in people with low socioeconomic status.

PATHOGENESIS:

Inflammation:

Inflammation of the lower respiratory tract has an important role in the pathogenesis of COPD. Following the exposure to tobacco smoke and other inhaled particles, there is a recruitment of inflammatory cells in the lungs and airways. Inflammatory cells seen are neutrophils, macrophages, eosinophils and lymphocytes. They cause lung injury and disrupt the normal mechanism of lung repair. Bronchoalveolar lavage (BAL) fluid collected from smokers show more macrophages when compared to non-smokers[2]

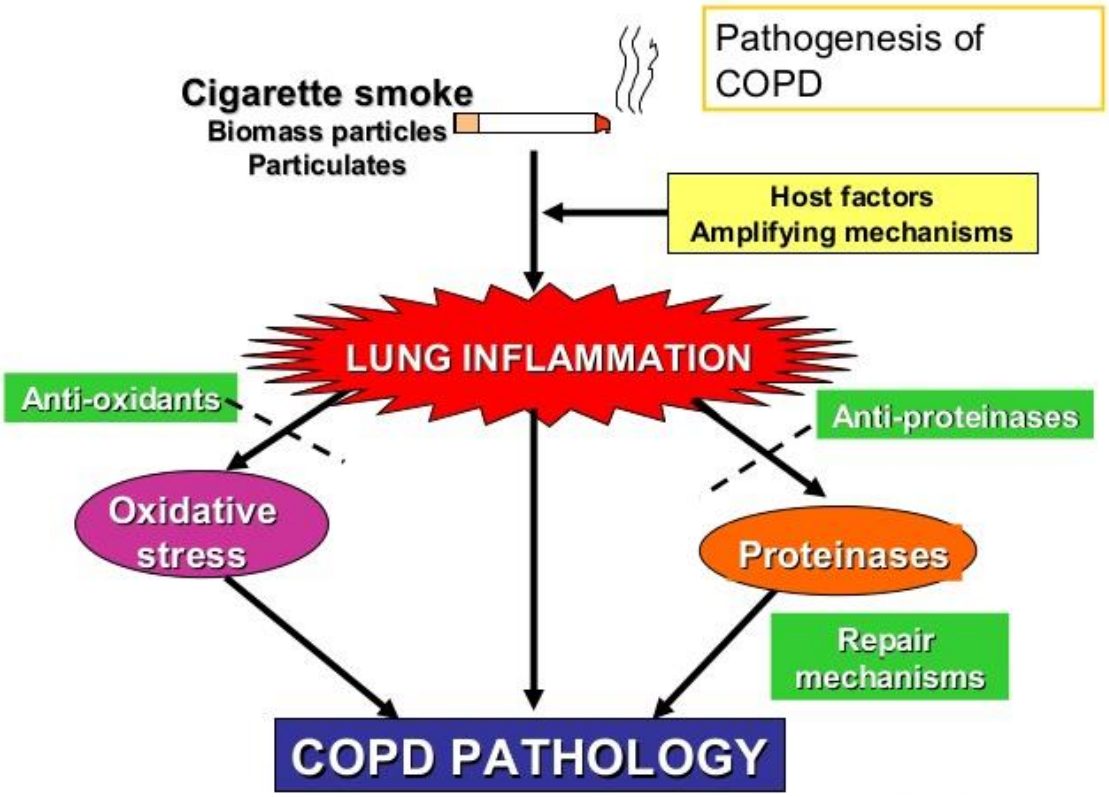
Proteinase and Antiprotease Imbalance:

In COPD, there is an imbalance between the production of proteinase and antiproteinase. Major proteinase that affects the lung parenchyma are neutrophil elastase, Proteinase 3, cathepsin B, cathepsin S, cathepsin L, MMP (Matrix Metalloproteinase).

Some of the antiproteinases are alpha 1 antitrypsin, Matrix metalloproteinase inhibitors, alpha 2 macroglobulin, Secretory leukocyte protease inhibitor(SLPI), Elafin and cystatin C. Neutrophil elastase causes

parenchymal destruction, hyperplasia of mucous glands and induces mucus hypersecretion.

Fig: Overview of COPD pathology:



Oxidative Stress

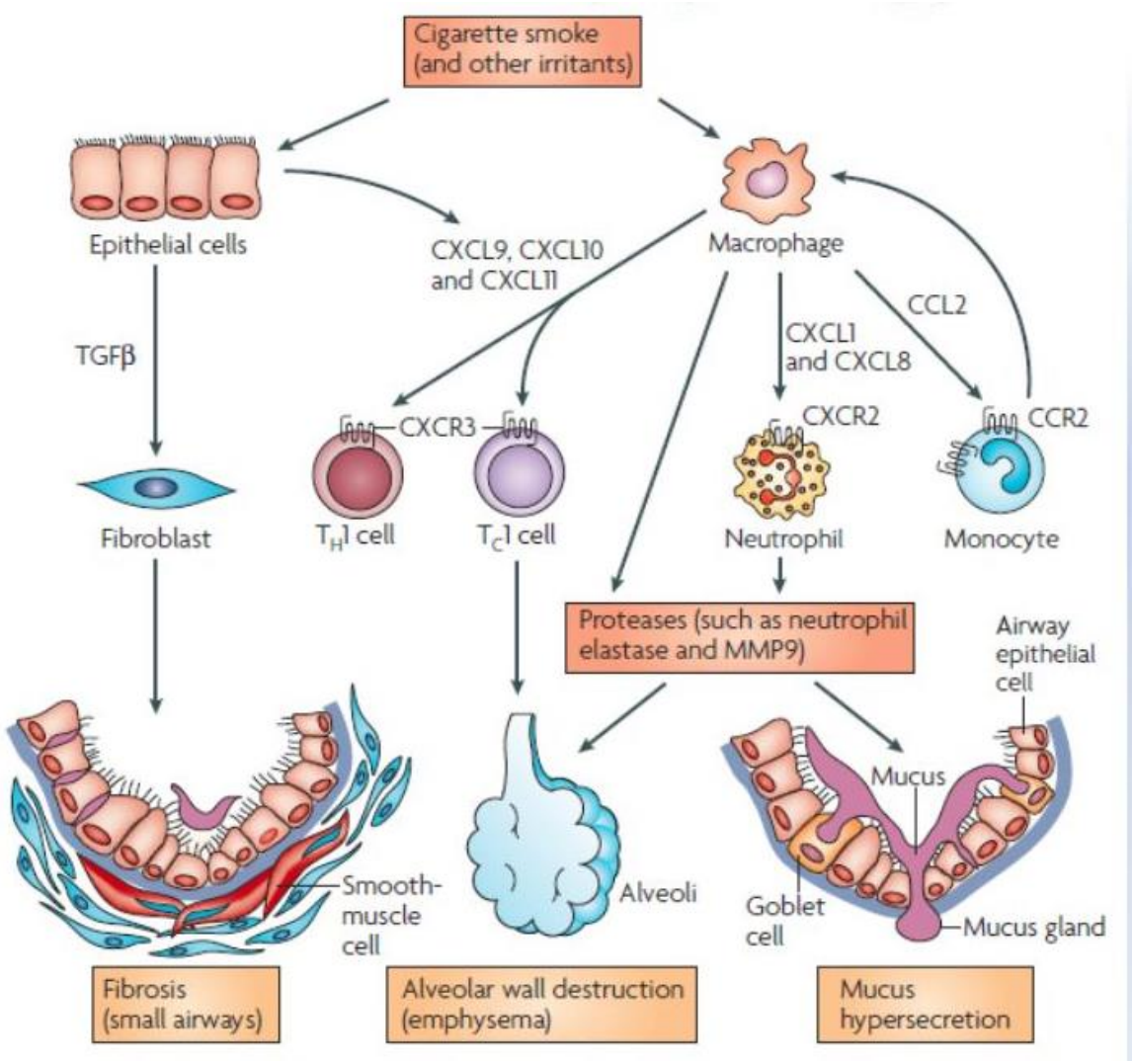
Cigarette smoke contains many chemicals that are reactive oxidant species. Also, the inflammation caused itself generates oxygen-free radicals leading to tissue destruction. In vitro study done by Schaberg et al showed that alveolar macrophages and airway neutrophils generate more oxygen free radicals such as hydrogen peroxide, hydroxyl radicals, and superoxide radicals in smokers than non-smokers.

Oxidative stress causes the damage of the extracellular matrix and inactivation of key anti-oxidant defences. Antioxidants generally protects against oxidative injury. Superoxide dismutase, Catalase, and glutathione peroxidase are some of the antioxidants that protects against oxidation injury. Copper and zinc dependent superoxide dismutase are found in cytoplasm and manganese dependent superoxide dismutase is found in mitochondria.

There can also be reduction of endogenous antioxidants in COPD, due to reduction in the levels of the transcription factor Nrf2 regulates many of the antioxidant genes.

Vitamin A and Vitamin E are present in epithelial lining fluid and act as antioxidants[2].

Fig : Pathogenesis of COPD



AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

TO ESTIMATE THE PREVALENCE OF

RENAL DYSFUNCTION IN

PATIENTS WITH

CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

COPD AND IT'S COMORBIDITIES:

COPD is a multisystem disease with inflammation at its peak leading on to mortality. The extent of the inflammatory reaction almost correlates with the severity of the disease.

Extrapulmonary comorbidities has an influence on the prognostic outcomes of the patients with COPD. Tobacco smoking is a common risk factor for many other associated comorbidities, including coronary heart disease, heart failure and lung cancer(12).

Various comorbidities associated with COPD are:

- Pulmonary hypertension
- Malnutrition
- Coronary artery disease
- Heart failure
- Lung cancer
- Systemic venous thromboembolism
- Peripheral muscle wasting
- Anxiety & depression

- Osteoporosis
- Metabolic syndrome
- Diabetes and hypertension
- Sleep disturbances
- Obstructive sleep apnea
- Peripheral vascular diseases
- Cognitive impairment

Extent of renal dysfunction associated with COPD is largely understudied. It could be a part of systemic inflammation or it could be due to the common risk factors associated with both these conditions such as age and tobacco use.

There are lot of other proposed mechanisms involved in the pathogenesis, which includes vascular cause, persistent hypercapnia itself drives the development of renal dysfunction.

SYSTEMIC INFLAMMATION IN COPD:

Chronic obstructive pulmonary disease is characterised by chronic inflammation of the pulmonary tissue. The extent of the inflammation is proportional to the severity of the disease.

The increase in inflammatory mediators in COPD has been thought be a part of "spill over" of the mediators from the pulmonary compartment which is mainly responsible for the inflammation present in the systemic circulation. The role of the spill over hypothesis has been further emphasized in many other researches by observing the relationship between the inflammatory mediators and pulmonary tissue-derived proteins.

The probable mechanism proposed in spill over hypothesis are(14) :

The Leakage of reactive oxygen species and stress induced cytokines into the systemic circulation. Preactivation of peripheral blood leukocytes that can result in aberrant homing and activation of inflammatory cells. Liberation of proinflammatory mediators by stromal cells and leucocytes present in the pulmonary tissues during progression of the disease.

The intensity of the inflammation in the systemic circulation is directly proportional to the poorer quality of life, degree of airflow limitation and exercise intolerance observed in COPD.(16) COPD can cause a low grade systemic inflammation due to hypoxia and various other mechanisms and

systemic inflammation in turn has propensity to adversely affect the clinical and functional characteristics of COPD.

The various mediators that take part in systemic inflammation are:

Cytokines

Interleukin-6:

Interleukin (IL)-6 is increased in the systemic circulation of patients with COPD, more commonly during exacerbations, and may account for the increase in circulating acute phase proteins such as C-reactive protein (CRP) found in patients with COPD as it induces the release of acute phase proteins from the liver [19]. The effects of circulating IL-6, apart from increasing acute phase proteins, are not yet certain but there is evidence that it may be associated with weakness of the skeletal muscle.

In an elderly population with or without airway obstruction, plasma IL-6 levels are related to decreased muscle strength measured by quadriceps strength and exercise capacity [20]. In rats, infusion of IL-6 induces both cardiac failure and skeletal muscle weakness [21]. Elevated levels of circulating IL-6 concentrations are found in several comorbid diseases.

Tumour necrosis factor-*α*:

Plasma tumour necrosis factor (TNF)-alpha and its soluble receptor are increased in patients with COPD [22–24], and TNF-alpha is also released from circulating cells in COPD patients with cachexia[25]. Circulating TNF-alpha

appears to be related, at least in part, to hypoxia [26]. Increased systemic TNF-alpha has been implicated as a mechanism of cachexia, skeletal muscle atrophy and weakness in COPD patients. Chronic administration of TNF-alpha in animals results in cachexia, leucocytosis, anaemia and infiltration of neutrophils into organs such as the heart, liver and spleen[27].

IL-1 β:

IL-1beta has also been linked to cachexia, but increased plasma levels or decreased levels of its endogenous antagonist IL-1 receptor antagonist have not been found in COPD, although there is an association between COPD and a polymorphism of the IL-1b gene [24].

Chemokines:

CXCL8 (IL-8) and other CXC chemokines play a significant role in neutrophil and monocyte recruitment in COPD patients, but circulating CXCL8 concentrations are also high in COPD patients and are related to skeletal muscle weakness [28].

Adipokines:

Leptin is an adipokine which is derived from fat cells that plays an important role in regulating energy balance, and in COPD patients, plasma concentrations tend to be lower than normal and there is a loss of diurnal variation [24], but its role in cachexia is not clear. On contrary to it, circulating

concentrations of ghrelin, a growth hormone-releasing peptide that increases food intake, is elevated in cachectic patients with COPD.

Acute phase proteins

CRP:

CRP is an acute phase protein, which is increased in the plasma of patients with COPD, particularly during acute exacerbations. In stable COPD patients, plasma concentrations are related to or cause mortality in mild to moderate patients, but not in severe and very severe patients . Increased CRP is also related to functional status and exercise capacity and appears to be an important predictor of body mass index (BMI)[22].Though CRP is related to forced expiratory volume in one second (FEV1) in cross-sectional studies, there is no association with the gradual decline of FEV1 in longitudinal studies . CRP is also increased in COPD acute exacerbations, due to viral or bacterial causes and a high concentration of CRP measured 2 weeks after a acute exacerbation predicts the likelihood of recurrent exacerbation [29].

The link between increased C-Reactive Protein and the prediction of cardiovascular risk has suggested that there might be an association between COPD and the increased prevalence of cardiovascular disease, but this relationship may be confounded by common risk factors, such as smoking. The functional role of CRP is uncertain. CRP binds to damaged tissues and leads to activation of the complement, resulting in endothelial dysfunction and tissue inflammation.

A small molecule inhibitor of CRP 1, 6-bis(phosphocholine)- hexane, neutralises the effects of CRP in animal models and therefore may be cardioprotective .The role of CRP has been questioned by the recent demonstration that transgenic overexpression of human CRP in mice is neither pro-inflammatory nor pro-atherogenic. Furthermore, there is evidence to suggest that CRP may play a significant role in innate defence against Streptococcus pneumoniae, so that inhibiting CRP could have detrimental effects, since this organism commonly colonises the lower airways of these COPD patients [30].

Fibrinogen:

Plasma fibrinogen levels are increased in COPD patients with recurrent exacerbations. An elevated plasma fibrinogen in a population is related to low FEV1 and an increased risk of exacerbation for COPD [31].

Serum amyloid A:

Serum amyloid (SA)-A is an acute phase reactant that is secreted by circulating pro-inflammatory cytokines from the liver but unlike CRP, also from inflamed tissue. Proteomic analysis of plasma has identified an increased levels of SA-A during acute exacerbations of COPD and its concentrations are correlated with the severity of exacerbations.

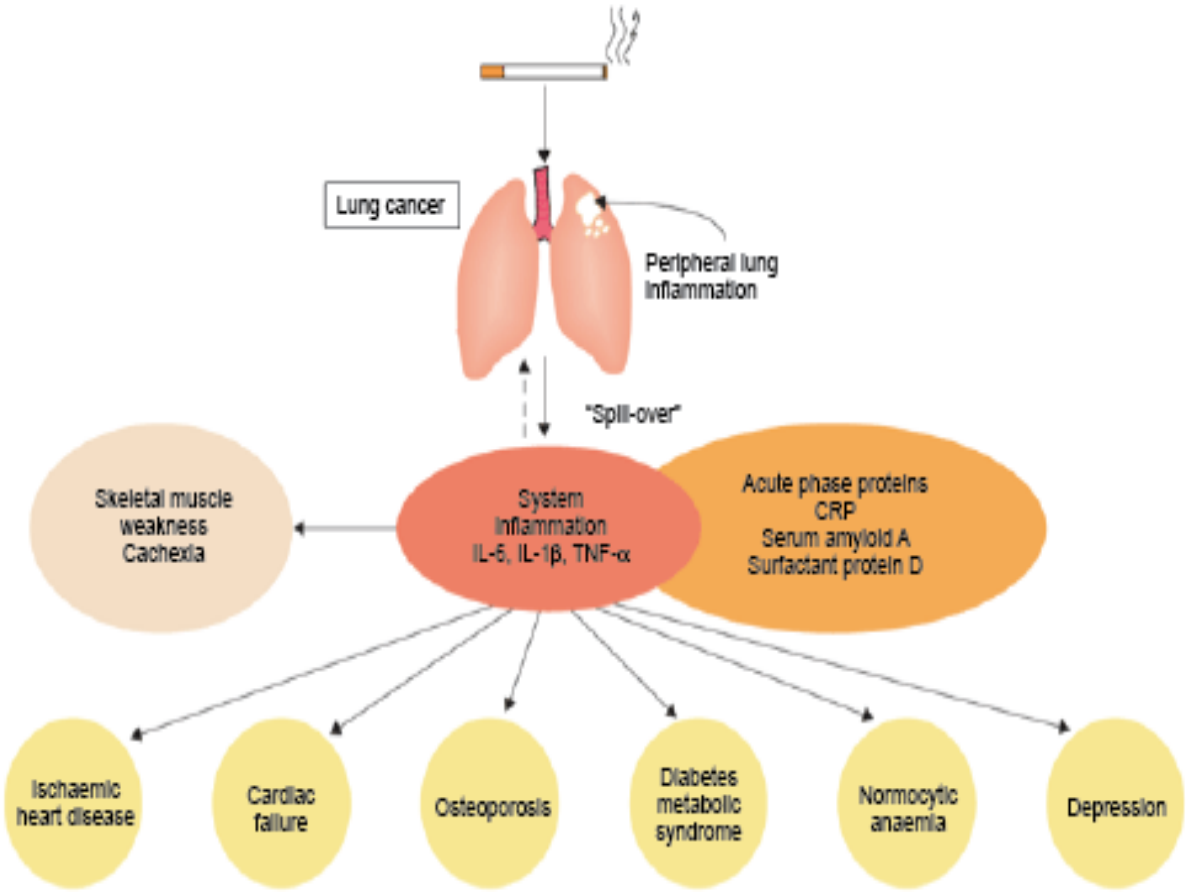
SA-A binds to Gram-negative bacteria and is part of the innate immune mechanism against bacterial infections, but it also has pro inflammatory effects, including the activation of monocytes, neutrophils and T-helper cell (Th) type

17. It has recently been discovered that SA-A is an activator of Toll-like receptor (TLR)2, resulting in activation of the inflammatory transcription factor nuclear factor (NF)-kB [32].

Surfactant protein D:

Surfactant protein (SP)-D is a glycoprotein of the collectin family and is secreted mainly by type II pneumocytes and plays a significant role in innate defence against microorganisms. Serum Surfactant protein (SP)-D levels are raised in patients with COPD and are better related to severity of the disease and symptoms than C-Reactive Protein [33]. Since Surfactant protein -D is derived mainly from peripheral lung tissue it provides a significant evidence that pulmonary inflammation can lead on to inflammatory changes in the systemic circulation rather than vice versa.

Fig : Systemic Inflammation in COPD



Circulating cells

Various abnormalities in circulating leukocytes have been reported in COPD patients. This may reflect systemic effects of inflammatory mediators derived from the lung on circulating cells or the bone marrow, or abnormalities in circulating cells may represent an underlying mechanism for amplifying inflammation in the lungs in response to cigarette smoking. Abnormalities in circulating leukocytes may have effects on organs other than the lung and therefore may be contributory to comorbidities. An integral part of the systemic inflammatory response is the activation of the bone marrow, which results in the release of leukocytes and platelets into the blood circulation. The leukocyte count is a predictor of total mortality independent of cigarette smoking in a large population-based study [34].

Monocytes:

Circulating monocytes in the lung are recruited by chemotactic factors such as CXCL1 (growth-related oncogene-a) and chemokine (C-C motif) ligand *(*CCL)-2 (monocyte chemotactic protein-1) into the lungs, where they differentiate into the macrophages that drive the disease . Monocytes from COPD patients show enhanced chemotactic responses to CXCL1 and the related chemokine CXCL7 (neutrophil activating protein 2) compared with monocytes from non-smokers and normal smokers, but normal responses to CXCL8 and CXCL5 (epithelial neutrophil activating peptide of 78kD). There is no increase in expression of their common receptor CXCR2 and the enhanced chemotactic

response to CXCL1 appears to be explained by increased turnover of CXCR2 [35].

This abnormality infers that there may be some intrinsic abnormality in circulating monocytes that could account for the greater accumulation of macrophages in the lungs of patients with COPD than in normal smokers. Circulating monocytes also release more matrix metalloproteinase (MMP)-9 spontaneously after lipopolysaccharide stimulation in cells from COPD patients compared with cells from non-smokers [36].

A major function of alveolar macrophages is phagocytosis of inhaled foreign particles, including bacteria. Alveolar macrophages show decreased phagocytosis of bacteria, such as H. influenzae and S. pneumoniae, which colonise the airways of COPD patients and may be involved in bacterial exacerbations and in driving the immune inflammatory response.

Monocytes from COPD patients have a similar phagocytic potential to cells from normal smokers and non-smokers, but when transformed into macrophages, show the same defect in phagocytosis as observed in alveolar macrophages. This does not appear to be a generalised defect in phagocytosis as the uptake of inert particles is not impaired. The defect cannot be accounted for by a defect in scavenger receptors and may be due to an intracellular defect in the phagocytic machinery required to take up bacteria. This suggests that there may be an intrinsic defect in monocytes once they differentiate to macrophages in the lungs that may result in impaired innate immunity against bacteria.

Neutrophils:

Circulating neutrophil numbers are not elevated in COPD patients but there is an inverse correlation between neutrophil numbers in the circulation and FEV1. There may be an increased turnover of neutrophils in smokers because neutrophils appear to marginate in the pulmonary circulation and are then replaced in the periphery by increased bone marrow production.

In rabbits, IL-6 and granulocyte-macrophage colonystimulating factor (GM-CSF) increase production from the bone marrow in association with down regulation of L-selectin on circulating neutrophils and promoting preferential sequestration in the pulmonary circulation. Chemotactic responses to formyl-methionyl-leucyl-phenylalanine and proteolytic activity of circulating neutrophils are raised in patients with COPD compared with normal smokers and non-smokers, indicating an abnormality in circulating cells [37].

Neutrophils from patients with COPD also show an increased production of reactive oxygen species in response to stimulatory agents. Although no significant difference in spontaneous apoptosis of circulating neutrophils has been reported in COPD patients compared with normal smokers, there is a decrease in L-selectin and an increase in Mac-1 (CD11b) expression .

Lymphocytes:

Changes in circulating lymphocytes are hard to interpret as they may reflect a recruitment of circulating lymphocytes into the lungs. In some studies

there is no major change in total T-cell population but an increase in B-lymphocytes in patients with COPD.

There is also a raise in apoptosis of peripheral T lymphocytes from COPD patients, with significantly increased expression of Fas, TNF-alpha and transforming growth factor (TGF)-beta. A more recent study reports an increase in CD8+ cells, particularly those expressing Fas, indicating that there can be an increase in apoptosis of CD8+ T-cells. Subset analysis has shown a slight increase in CD4+ cells expressing interferon (IFN)-c and a decrease in cells expressing IL-4, indicating Th1 predominance in the peripheral circulation, with no changes in CD8+ cell subsets. Circulating T-cells are increased in normal smokers but not in patients with COPD [38].

Natural killer cells:

A reduction of cytotoxic and phagocytic function of circulating natural killer cells has been reported in COPD, but the significance of this observation is uncertain.

SYSTEMIC MANIFESTATIONS OF COPD:

COPD AND RENAL DYSFUNCTION:

It is largely unknown to which extent COPD is associated with renal dysfunction.

A proportion of patients with COPD has diminished muscular mass, and thus, serum creatinine might be falsely low as the result of decreased release of creatinine. Also, Chronic Renal Failure (CRF) may be associated with normal creatinine levels, a condition known as unrecognized or concealed CRF. The association between COPD and CRF may be explained by several factors.

It was observed that renal arteriolar resistances are increased in patients with COPD, because of the increase in the local adrenergic discharge due to Carbon dioxide retention. In the early stages of COPD, perfusion of the kidneys are usually normal, but as the disease progresses, particularly as Carbondioxide retention develops, blood flow to the renal system gradually decreases. PaCO2 has been found to correlate inversely with effective renal plasma flow and with the ability of sodium and water excretion. Increase in Carbondioxide levels may cause constriction of renal blood vessels directly and indirectly by stimulating sympathetic system as detected by elevated levels of norepinephrine[47-48].

Nicotine in the smoke and few heavy metals such as lead and cadmium, which are components of smoke, are the risk factors in common for COPD and renal dysfunction. Nicotine causes nephropathies with an increased incidence of microalbuminuria progressing to proteinuria[49].

COPD is known as a cause of systemic inflammation. Pro-inflammatory cytokines, especially tumour necrosis factor-alpha, play a significant role in the disease process. This systemic inflammatory state in patients with COPD is associated with the increased risk of cardiac injury. In addition to pulmonary inflammation, several other parts of the body are affected resulting in decreased muscle mass, weight loss, diabetes, atherosclerosis, osteoporosis and renal dysfunction. So the systemic inflammatory reaction seen in patients with COPD might explain the association between COPD and CRF[50]. Also, as a result of the muscle wasting and reduced muscular mass frequently occurring in COPD patients; serum creatinine levels might be falsely low as the result of decreased creatine release and the GFR may be reduced despite normal creatinine concentration (concealed CRF).

Pulmonary hypertension secondary to COPD, may be associated with the progression of kidney disease. Fifth; coronary artery disease, which is highly prevalent in patients with COPD, is associated with vascular kidney disease[51].

The prevalence of renal dysfunction in various studies performed earlier are:

Ibrahim l.Elmahallawy et al [52] reported an increased incidence of 46% of renal dysfunction among them prevalence of overt renal failure was 20% and prevalence of concealed renal failure was 26%.

Raffaele Antonelli Incalzi et all [53] reported an incidence of 43% of renal dysfunction among them prevalence of overt renal failure was 22.2% and prevalence of concealed renal failure was 20.8%.

Takayuki Yoshizawa et all [54] found that 31% of the study population developed renal dysfunction.

Sharanya et al [55] reported an incidence of 37% of renal dysfunction among COPD patients.

Bjarte Gjerde et all [56] had a prevalence of 9.6% in Female COPD patients and 5.1% in male COPD patients.

COPD AND CARDIOVASCULAR DISEASE:

The relationship that exists between the lungs and the heart is such that any dysfunction that impacts either lung or heart is likely to have consequences on the other. This relationship is important in patients with COPD and can be summarised in two types of association. First, one correlates the pathogenesis that share similar risks, such as cigarette smoke and coronary artery disease (CAD), or congestive heart failure and COPD; and second, those which can cause dysfunction of the cardiovascular system from primary pulmonary disease, such as secondary pulmonary hypertension and ventricular dysfunction due to increased intra-thoracic mechanical loads.

In the Lung Health Trial, which included almost six thousand patients and followed them over fourteen years, FEV1 was an independent predictor of the probability of dying from a coronary artery disease. However, it has been proved that the risk of myocardial infarction increases independent of smoking habit in patients with COPD.

The plaques seen in atherosclerosis show a low grade inflammatory reaction, with elevated numbers of macrophages and IFN -γ secreting Th1 lymphocytes, similar to the inflammatory reaction seen in patients with COPD. Though the strength of the associations and the definitive mechanisms responsible have not been entirely elucidated, evidences suggest that patients with COPD should be screened for the presence of coronary artery disease.

COPD AND MUSCLE DYSFUNCTION:

Skeletal muscle weakness is one of the major systemic effects of COPD and is often accompanied by loss of fat-free mass (FFM). In chronic illnesses like COPD, loss of muscle mass occurs at a very slower rate. A slow yet substantial loss of muscle mass can be found during ageing process,called as sarcopenia. Data from human studies indicate that atrophy of skeletal muscles is apparent in patients with COPD and is specific to muscle fibre type IIA/IIx[40].

Furthermore, these abnormalities may be related to respiratory function, exercise intolerance, health status, healthcare resource utilisation and mortality. Muscle wasting is associated with decreased muscle strength, which in turn is a

determinant of exercise capacity in COPD patients independent of disease severity.

COPD AND OSTEOPROSIS:

Several researches have shown a high prevalence of osteoporosis and low bone mineral density (BMD) in COPD patients, even in earlier stages of disease. More than half of patients with COPD recruited for the large TORCH (Towards a Revolution in COPD Health) trial (6,000 patients) had osteopenia or osteoporosis as determined by dual-energy radiograph absorptiometry (Dexa). Fractures involving vertebra are relatively common among COPD patients and the resultant increased kyphosis may further reduce pulmonary function [41].

COPD AND DEPRESSION:

Due to the physical impairment, COPD patients are frequently isolated and unable to engage in social activities. Anxiety and depression are common in patients with COPD and appear to be more prevalent than in other chronic diseases. Depression that is clinically relevant are estimated to occur in 10–80% of all COPD patients.

The pathophysiology for depression in patients with COPD are not known and likely to be multifactorial. There is a recent evidence that a widespread systemic inflammation may result in depression and IL-6 appears to play a significant role in humans and in animal models of depression [42].

COPD AND LUNG CANCER:

Patients with COPD are three to four times more likely to develop lung cancer than smokers with normal lung function and lung cancer is the most common cause of death in COPD patients, particularly those with stage four disease.

Interestingly, lung cancer was also common in patients with COPD who are non-smokers, in a large prospective trial of almost half a million non-smokers. Female gender may have a higher risk of COPD and lung cancer, possibly due to hormone related metabolism of carcinogens in tobacco smoke [43].

COPD AND DIABETS:

Previous researches show that there is an increased prevalence of diabetes among patients with COPD (relative risk 1.5–1.8), even in patients with mild degree of disease [1, 150]. The reasons for this association are not yet clearly explained. It is unlikely to be explained by high doses of inhaled corticosteroids, as patients who were not on steroids with mild disease also have an elevated risk of diabetes.

Interestingly, patients with asthma do not have an raised risk of developing diabetes, so this may suggest a link to the different pattern of inflammation in COPD compared with asthma and may be related to inflammation seen in the systemic circulation. Pro -inflammatory cytokines,

including TNF-alpha and IL-6, may induce insulin resistance by blocking signalling through the insulin receptor and increase the risk of type 2 diabetes.

COPD AND HYPERTENSION:

The incidence of hypertension is approximately 6-50% and depends upon the level of airflow obstruction. A recently done INDACO study demonstrated a 53% incidence of hypertension.

The pathological mechanisms responsible for hypertension in COPD are Vasoconstriction as a result of hypoxia, Free radical injury, Endothelial dysfunction and Arterial stiffness.

COPD AND OBSTRUCTIVE SLEEP APNEA:

Epidemiological studies had found that,20% of patients with obstructive sleep apnoea (OSA) also have associated COPD, whereas 10% of patients with COPD have OSA independent of the severity of the disease . OSA patients also share several of the comorbidities of COPD, such as endothelial dysfunction, diabetes, cardiac failure and metabolic syndrome . There is a recent evidence that obstructive sleep apnoea patients have upper airway inflammation, as well as systemic inflammation and oxidative stress [45].

COPD AND METABOLIC SYNDROME:

The mechanism responsible for development of COPD and the Metabolic syndrome is primarily due to systemic inflammatory reaction[46].

Several mechanisms has been hypothesised regarding the association between obesity and airflow limitation

(a) Decrease in the compliance of the lung and the chest.

(b) Expiratory airflow limitation and Small airway dysfunction.

(c) Variable reduction in respiratory muscle strength.

(d) Increased workload of breathing.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN:

Cross sectional observational study.

STUDY PERIOD:

12 months from May 2017 to April 2018

SAMPLING METHOD:

Done by Consecutive sampling method.

STUDY CENTRE:

Rajiv Gandhi Government General Hospital, Park Town, Chennai.

SUBJECT SELECTION:

Inclusion criteria:

- Patients Attending thoracic medicine OP and diagnosed as a case of COPD according to GOLD 2017 guidelines with post bronchodilator FEV1/FVC less than 0.70
- Patients willing to participate in the study and give informed written consent.

Exclusion criteria:

- COPD with an acute exacerbation in past 6 weeks.
- Known cases of lung diseases other than COPD
- Known cases of CKD

SAMPLE SIZE:

364 patients who were diagnosed as COPD and those who satisfied the inclusion and exclusion criteria were enrolled in the study.

DATA COLLECTION:

The data were collected from the patient are:

- Name
- Age
- Sex
- Occupation

Detailed clinical history was collected which included

- History of cough with expectoration and wheeze with their duration.
- History of exacerbations and hospitalization in the past 1 year (exacerbations when patient needed to attend a health care setup because of symptoms which lead to increase in the dose or addition of a medication)
- Histroy regarding severity of symptoms as obtained by Modified Medical Research Council grades(mMRC) and using COPD assessment Test (CAT)
- Previous history of co-morbid illness like diabetes mellitus, hypertension.
- Smoking history
- History of exposure to biomass and noxious stimulus

Severity of symptoms:

Severity of symptoms as perceived by the patient was assesed using Modified Medical Research Council grades (mMRC)

Modified Medical Research Council grades (mMRC) :

Modified medical research council scale was used to assess the severity of dyspnoea. It quantifies the disability associated with breathlessness by identifying when does the breathlessness occurs (Grades 0 and 1) or by quantifying the associated exercise impairment (Grades 2–4) The mMRC grades were self-administered asking patients to choose the description that best suited to their condition.

Table : Modified Medical Research Council grades

GRADE	DESCRIPTION
0	I only get breathless with strenuous excersice
1	I get short of breath with hurrying on the level or walking up a slight hill
2	I walk slower than people of the same age group on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
3	I stop for breath after walking about 100 yards or after a few minutes on the level
4	I am too breathless to leave the house or I am breathless when dressing

CAT SCORE:

The COPD assessment test is a questionnaire that is completed by the patient to assess the status of health and the severity in patients with COPD. The questionnaire was translated to the study site language and then translated back to English. It is composed of eight questions each presented as a six-point (0-5) differential scale with a total score out of 40. The clinical impact of the disease is graded as follows:

- 0-10 – mild
- 11-20 – moderate
- 21-30 – severe
- 31-40 – very severe

How is your COPD?

For each item below, place a mark (√) in the box that best describes your experience.

Example: I am very happy | 0 | √ 1 | 2 | 3 | 4 | 5 | I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	☐
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	☐
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	☐
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	☐
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	☐
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	☐
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	☐
I have lots of energy	0 1 2 3 4 5	I have no energy at all	☐

SCORE ☐☐

SMOKING STATUS:

Smoking status of the patient was recorded using CDC guidelines definition: [51]

Current smoker - who has smoked greater than 100 cigarettes in his lifetime and now smokes every day or some days

Former smoker - who has smoked greater than 100 cigarettes in their lifetime and does not currently smoke.

Never smoker - who has not smoked greater than 100 cigarettes in their lifetime.

Number of pack-years was calculated by the following formula:

Number of pack-years = (number of *cigarettes*/ bidi smoked per day/20) × number of Years smoked [14].

Body Mass Index:

Body Mass Index (BMI) was calculated from the height and the weight of the patient using the formula

BMI = Weight in kg / (Height in m)²

Table : Interpretation of nutritional status using BMI

BMI	NUTRITIONAL STATUS
<18.5	Under weight
18.5-24.9	Normal
25-29.9	Overweight
≥30	Obese

Investigations including:

- Chest X ray PA view
- Haemoglobin
- Renal function test
- eGFR calculation were done.

Pulmonary Function Test:

Pulmonary function test was done for all patients who were enrolled. The test was performed in accordance with the criteria set by American Thoracic Society using Easyone Spirometer. The instrument was calibrated daily as recommended. The procedure was explained to all the patients clearly before the test is done. Any recent history of smoking, illness, medications were enquired and the height and weight of the patient was recorded. All participants were kept in the sitting posture for the procedure.

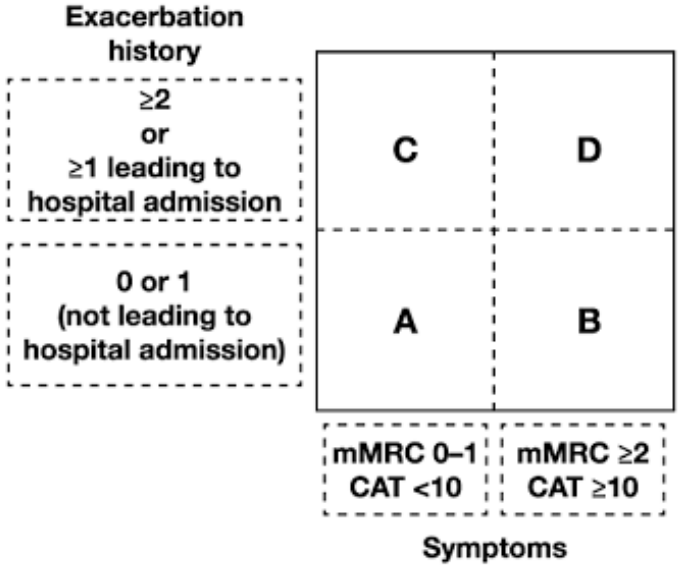
All participants were instructed and demonstrated to hold the head in slightly elevated manner, position the mouthpiece and close the lips, inhale completely and rapidly and then exhale maximally until no more air can be expelled out.

Instructions were repeated as necessary. Throughout the manoeuvre, subjects were encouraged to blast out and exhale using appropriate body languages and phrases. The test was stopped whenever they complained of distress or dizziness. The test was repeated till at least three trials with two acceptable and reproducible tests for both FEV1 and FVC were obtained. Measurements were made before and after at least 15 minutes of two puffs of salbutamol (200 microgram) administered using metered dose inhaler with a volumetric spacer. The degree of airflow obstruction was assessed using GOLD guidelines.

Table : Severity of airflow limitation as per GOLD guidelines[1]

GOLD 1	Mild	FEV1≥ 80% PREDICTED
GOLD 2	Moderate	50%≤ FEV1 <80% PREDICTED
GOLD 3	Severe	30%≤ FEV1 < 50% PREDICTED
GOLD 4	Very severe	FEV1 < 30% PREDICTED

Table : GOLD Category



Serum Creatinine:

Serum creatinine in blood is an important indicator of renal health because, it is an easily measurable byproduct of muscle metabolism. It is excreted unchanged by the kidneys.

Most clinical laboratories now align their creatinine measurements against a new standardized Isotope Dilution Mass Spectrometry (IDMS) method to measure serum creatinine

Serum creatinine value of 1.2 mg/dl is the cut off value, above which is defined as the patient has renal dysfunction.

Estimated Glomerular Filtration Rate:

While recognizing the inadequancies of plasma creatinine and a 24hr creatininie clearance, the National Kidney Foundation Diseases outcomes Quality Initiative (K-DOQI) recommends the use of estimates of GFR calculated from prediction equations based on plasma/serum creatinine.

Earlier various equations were used to calculate the GFR, now CKD-Epidemiology Collaboration group (CKD-EPI) developed a new equation in 2009, which is the most accepted equation used at the present.

$GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black]

- Scr is serum creatinine (mg/dL),
- κ is 0.7 for females and 0.9 for males,
- α is -0.329 for females and -0.411 for males,
- min indicates the minimum of Scr/κ or 1,
- and max indicates the maximum of Scr/κ or 1

Renal dysfunction is said to be present when the estimated glomerular filtration rates are < 60 ml/min/1.73m^2.

OBSERVATION AND RESULTS

RESULTS

PATIENT CHARACTERISTICS:

A total number of 364 COPD patients were included in the study after satisfying the inclusion and exclusion criteria.

AGE DISTRIBUTION

The number of patients in the age groups 41-49 is 25(6.9%), 50-59 is 98(26.9%), 60-69 is 185(50.8%), ≥ 70 is 56(15.4%).

Table : Age distribution

Age range	Frequency	%
40-49	25	6.9%
50-59	98	26.9%
60-69	185	50.8%
≥70	56	15.4%

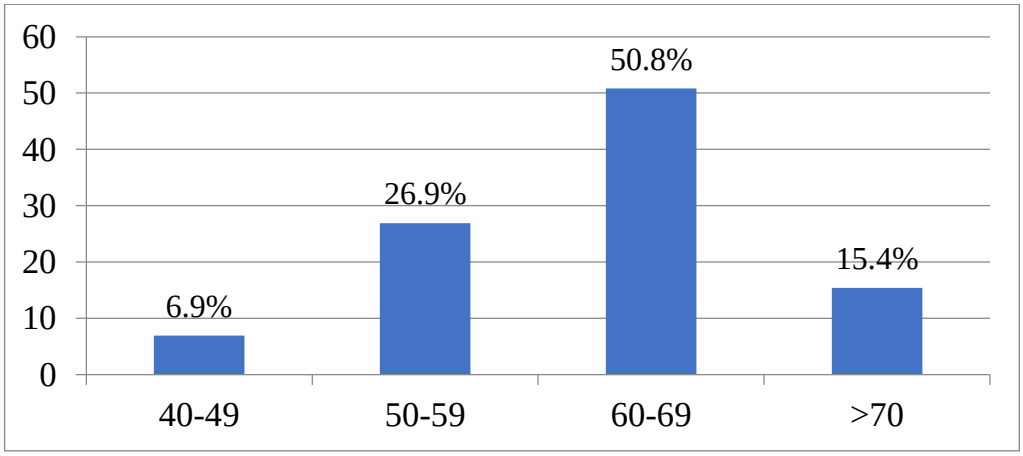


Fig : AGE DISTRIBUTION

GENDER DISTRIBUTION:

Among 364 patients enrolled in the study 55 were females and 309 were males.

Table : Gender distribution

	FREQUENCY	%
MALE	309	84.9%
FEMALE	55	15.1%
TOTAL	364	100%

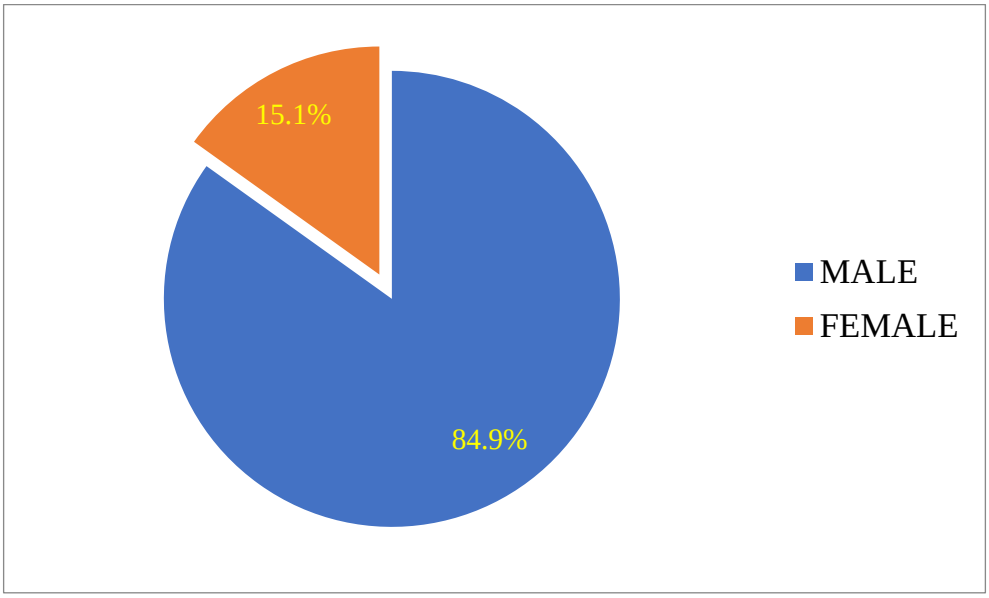


Fig : Distribution based on Gender

mMRC GRADING OF DYSPNEA:

The severity of breathlessness was graded based on mMRC grading of dyspnea. Of the 364 patients, none had grade 4, while majority were in grade 2 or 3mMRC.The percentage of patients with grade 1, 2 and 3 were 10.2%, 62.4%, 27.5% respectively.

Table : mMRC grading of dyspnea

mMRC Grade	FREQ	%
1	37	10.2%
2	227	62.4%
3	100	27.5%
TOTAL	364	100%

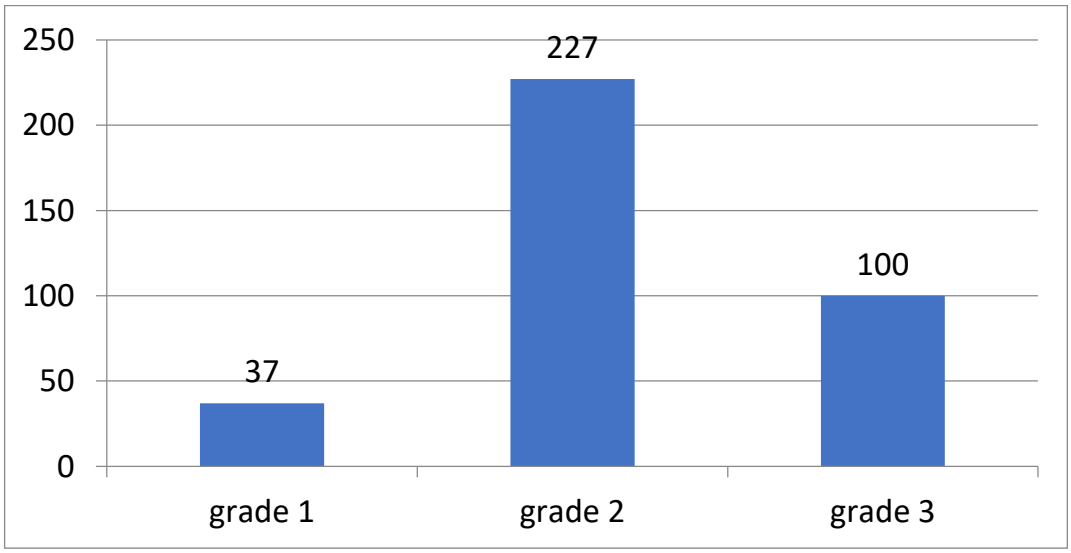


Fig :Distribution based on mMRC dyspnea grading

CAT SCORE:

In the study population 213 of them had CAT score of less than 10 and 151 of them had CAT score of more than 10.

Table : Distribution of patients by CAT score

CAT score	FREQ	%
<10	213	58.5%
≥ 10	151	41.5%
Total	364	100%

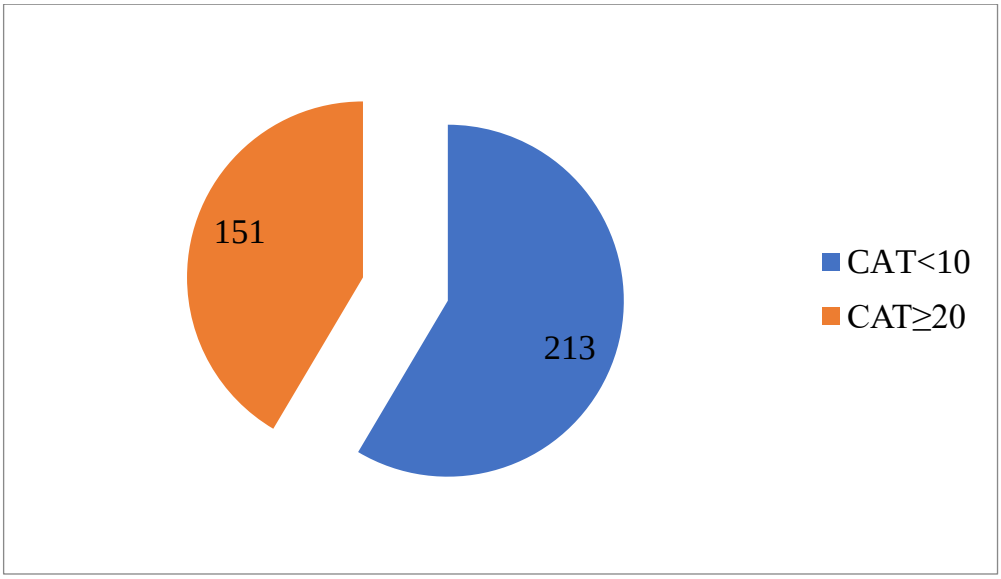


Fig : Distribution of patients by CAT score

PREVIOUS HOSPITALISATON IN THE STUDY POPULATION:

Among 364 study population, 299 patients didn't have any hospitalisation in the past, 65 patients had more than or eaual to one hospitalisation.

Table : Distribution of patients by previous hospitalisation

No.of.Hospitalisation	FREQ	%
0	299	82.1%
≥1	65	17.9%
TOTAL	364	100%

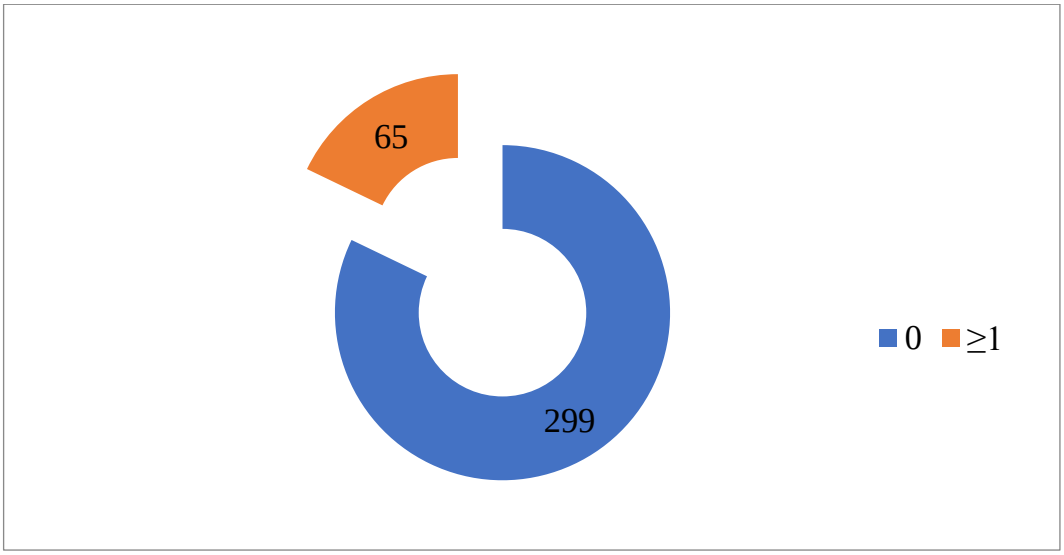


Fig : Distribution of patients based on past history of hospitalisations

DEGREE OF AIRFLOW LIMITATION IN STUDY POPULATION:

In our study, 8 patients were in mild COPD (>80% predicted). 44 of them were in very severe COPD (<30% predicted), 123 had moderate COPD(50% to 80% predicted) and majority i.e.,189 had severe airflow limitation(30% to 50%).

Table : Degree of airflow limitation

Degree of airflow limitation	FREQ	%
Mild	8	2.2%
Moderate	123	33.8%
Severe	189	51.9%
Very severe	44	12.1%
Total	364	100%

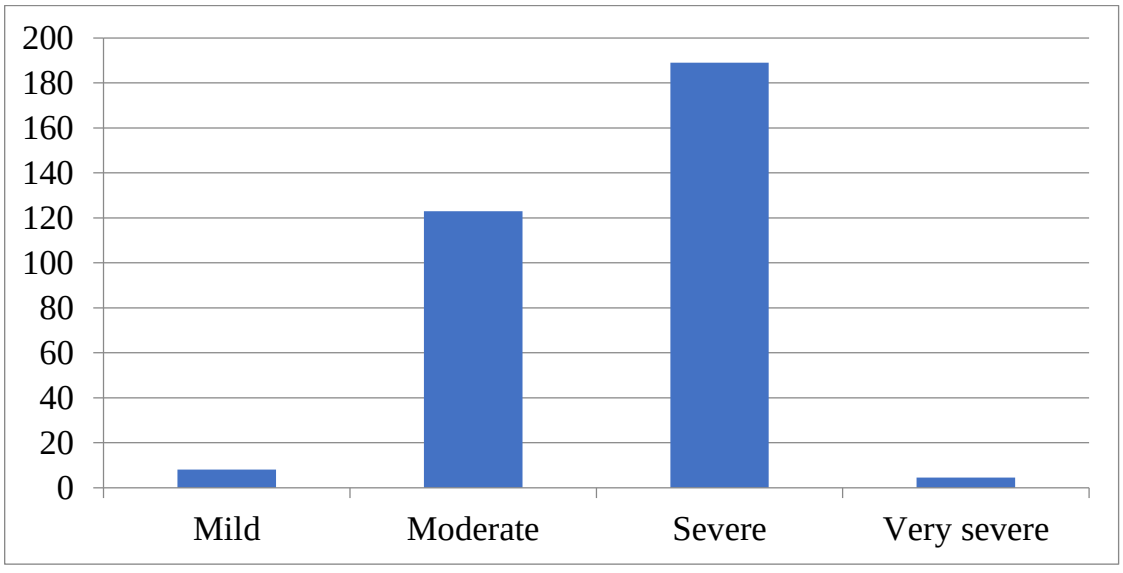


Fig : Distribution of patients by airflow limitation(FEV1)

GOLD CATEGORY AMONG THE STUDY POPULATION :

Among the study population 30 patients(8.2%) were in GOLD Category A, 269 patients(73.9%) were in GOLD Category B and 65 were in GOLD Category D.

Table: GOLD Category

GOLD Category	FREQ	%
CATEGORY A	30	8.2%
CATEGORY B	269	73.9%
CATEGORY D	65	17.9%
TOTAL	364	100%

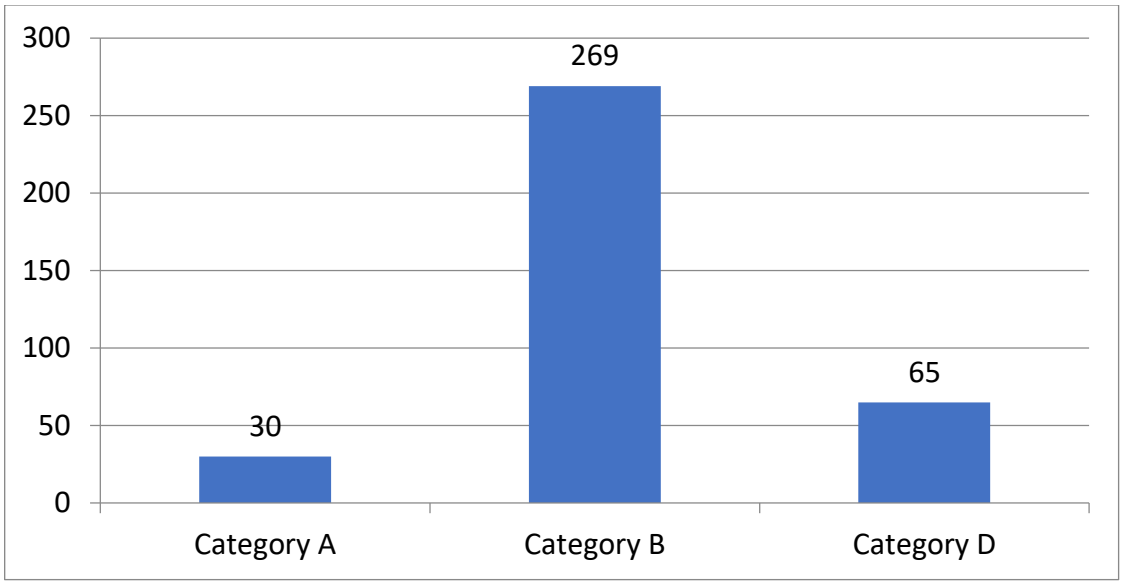


Fig : Distribution of patients by GOLD Category

SMOKING STATUS IN THE STUDY POPULATION:

In the study population 116 patients were non-smokers and almost 33%(121) had pack years of greater than 40

Table : Distribution of patients by pack years

PACK YEARS	FREQ	%
0	116	31.9%
1-20	62	17%
21-40	65	17.9%
≥40	121	33.2%
TOTAL	364	100%

BODY MASS INDEX OF THE POPULATI

Among the study population 223 were in the normal range, 67 were under weight, 70 were overweight, 4 were obese.

Table : BMI Distribution

BMI RANGE	FREQ	%
<18.5 - Under weight	67	18.4%
18.5-24.9 - Normal	223	61.3%
25-29.9 – Over weight	70	19.2%
≥30 - Obese	4	1.1%

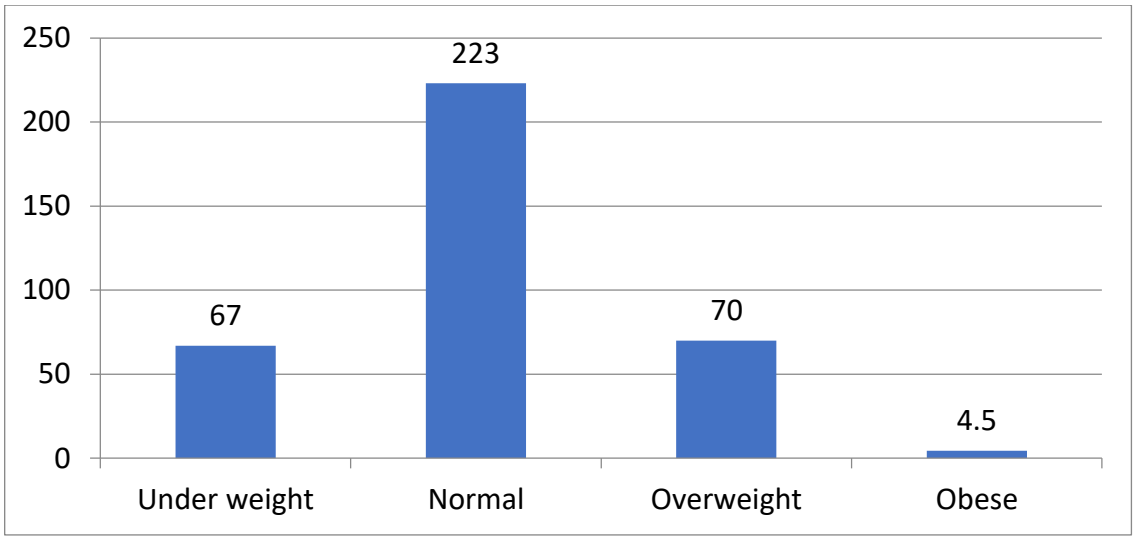


Fig : Distribution based on BMI

PRESENCE OF COMORBIDITIES:

Diabetes mellitus

In our study group 47(12.9%) were diabetics.

Table : Distribution of patients by Diabetes

DM	FREQ	%
YES	47	12.9%
NO	317	87.1%

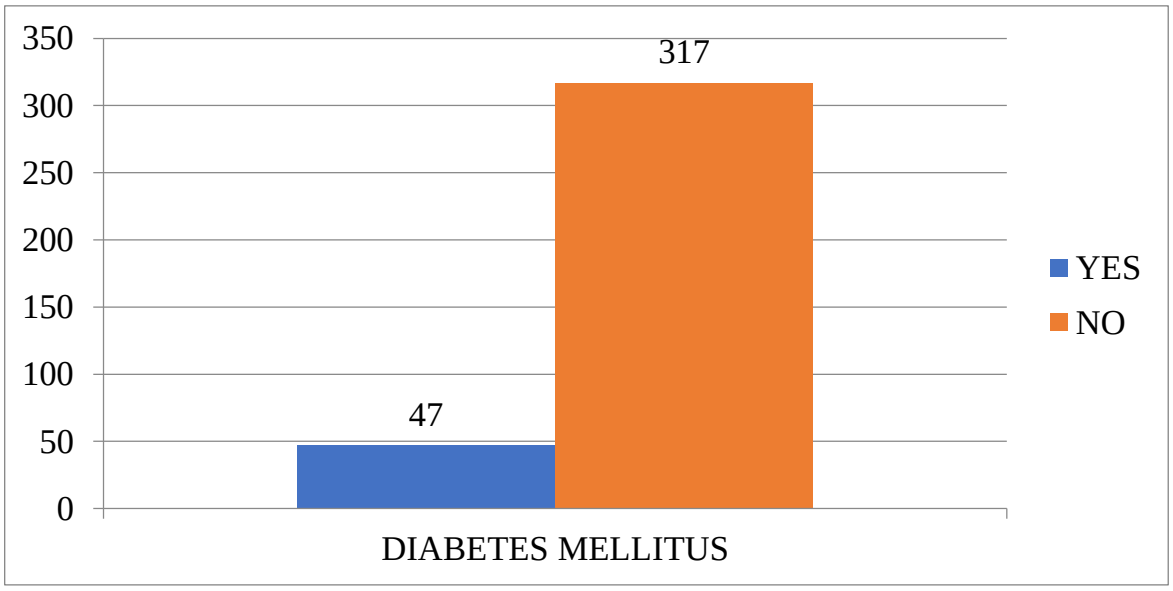


Fig: Distribution of patients based on Diabetes

HYPERTENSION:

IN our study group 62(17%) were hypertensives.

Table: Distribution of patients by Hypertension

HT	FREQ	%
YES	62	17.0%
NO	302	83.0%

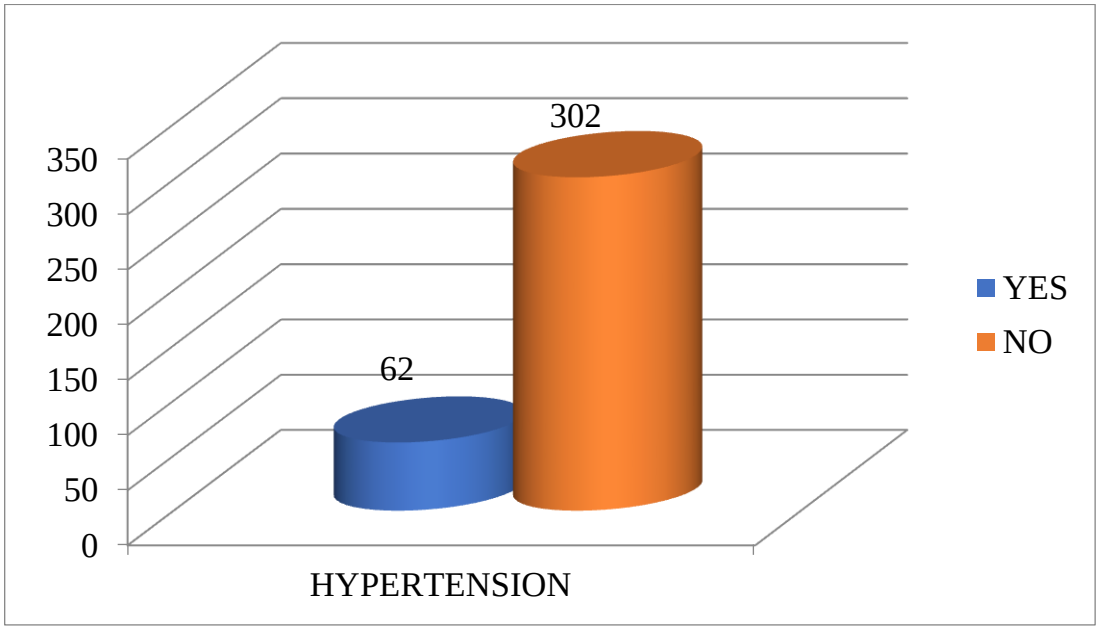


Fig: Distribution of patients based on Hypertension

DISTRIBUTION BASED ON HAEMOGLOBIN VALUES:

In our study population 53.3%(194) were anemic and 170 (46.7%) were having haemoglobin values above 10 mg/dl.

Table : DISTRIBUTION BASED ON HAEMOGLOBIN VALUES

HEMOGLOBIN VALUE	FREQ	%
≤10 mg/dl	194	53.3%
>10 mg/dl	170	46.7%
TOTAL	364	100%

SERUM CREATININE:

In the study population 67(18.4%) had creatinine values more than 1.2 and the remaining 297 (81.6%) had creatinine values less than or equal to 1.2

Table : Distribution of patients by serum creatinine

CREATININE	FREQ	%
>1.2	67	18.4%
≤1.2	297	81.6%
TOTAL	364	100%

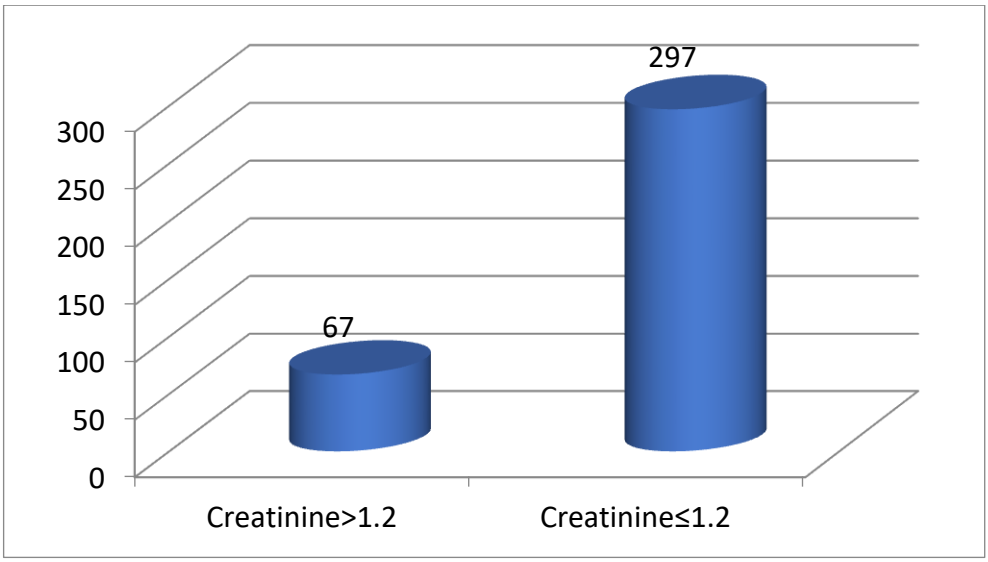


Fig : Distribution based on serum creatinine

PREVALANCE OF RENAL DYSFUNCTION MY STUDY POPULATION:

	FREQ	**%**
OVERT RENAL FAILURE	67	18.4%
CONCEALED RENAL FAILURE	24	6.6%
NORMAL RENAL FUNCTION	273	75%
TOTAL	364	100%

Among the study population of 364 patients 25% of them had renal dysfunction.

Among them 18.4% had overt renal failure(e GFR<60, Creatinine>1.2) and 6.6%had concealed renal failure (e GFR<60, Creatinine<1.2). 273 COPD patients had normal renal function.

Table: Association of various factors with the development of Renal dysfunction in COPD patients.

		RENAL_FAILURE						p value by Chi sq test
		OVERT		CONCEALED		NORMAL		
		Freq	%	Freq	%	Freq	%	
AGE	40 - 49 years	0	0.0%	0	0.0%	25	100.0%	0.001
	50 - 59 years	9	9.2%	0	0.0%	89	90.8%	
	60 - 69 years	58	31.4%	11	5.9%	116	62.7%	
	>=70 years	0	0.0%	13	23.2 %	43	76.8%	
GENDER	Male	67	21.7%	13	4.2%	229	74.1%	0.003
	Female	0	0.0%	11	20.0 %	44	80.0%	
Mmrcgrade	1	8	21.6%	0	0.0%	29	78.4%	0.017
	2	45	19.8%	21	9.3%	161	70.9%	
	3	14	14.0%	3	3.0%	83	83.0%	
CAT	< 10	41	19.2%	10	4.7%	162	76.1%	0.214
	>=10	26	17.2%	14	9.3%	111	73.5%	
PREVIOUSHOSPITALISATION	0	54	18.1%	17	5.7%	228	76.3%	0.047
	1	13	20.0%	7	10.8 %	45	69.2%	
SEVERITY	1	3	37.5%	0	0.0%	5	62.5%	0.035
	2	23	18.7%	3	2.4%	97	78.9%	
	3	29	15.3%	21	11.1 %	139	73.5%	
	4	12	27.3%	0	0.0%	32	72.7%	
CATEGORY	A	8	26.7%	0	0.0%	22	73.3%	0.051
	B	46	17.1%	17	6.3%	206	76.6%	
	D	13	20.0%	7	10.8 %	45	69.2%	
BMI	UNDERWEIGHT	5	7.5%	7	10.4 %	55	82.1%	0.041
	NORMAL	53	23.8%	14	6.3%	156	70.0%	
	OVERWEIGHT	9	12.9%	3	4.3%	58	82.9%	
	OBESE	0	0.0%	0	0.0%	4	100.0%	

PACK YEARS	**0**	8	6.9%	14	12.1 %	94	81.0%	0.002
	1 – 20	18	29.0%	3	4.8%	41	66.1%	
	21 – 40	13	20.0%	0	0.0%	52	80.0%	
	>= 40	28	23.1%	7	5.8%	86	71.1%	
DM	**Yes**	0	0.0%	13	27.7 %	34	72.3%	0.028
	No	67	21.1%	11	3.5%	239	75.4%	
HT	**Yes**	12	19.4%	9	14.5 %	41	66.1%	0.038
	No	55	18.2%	15	5.0%	232	76.8%	
CAD	**Yes**	3	25.0%	0	0.0%	9	75.0%	0.15
	No	64	18.2%	24	6.8%	264	75.0%	
Hb	**Anemic**	32	16.5%	11	5.7%	151	77.8%	0.025
	Not Anemic	35	20.6%	13	7.6%	122	71.8%	

Risk factors associated with development of renal dysfunction in COPD patients:

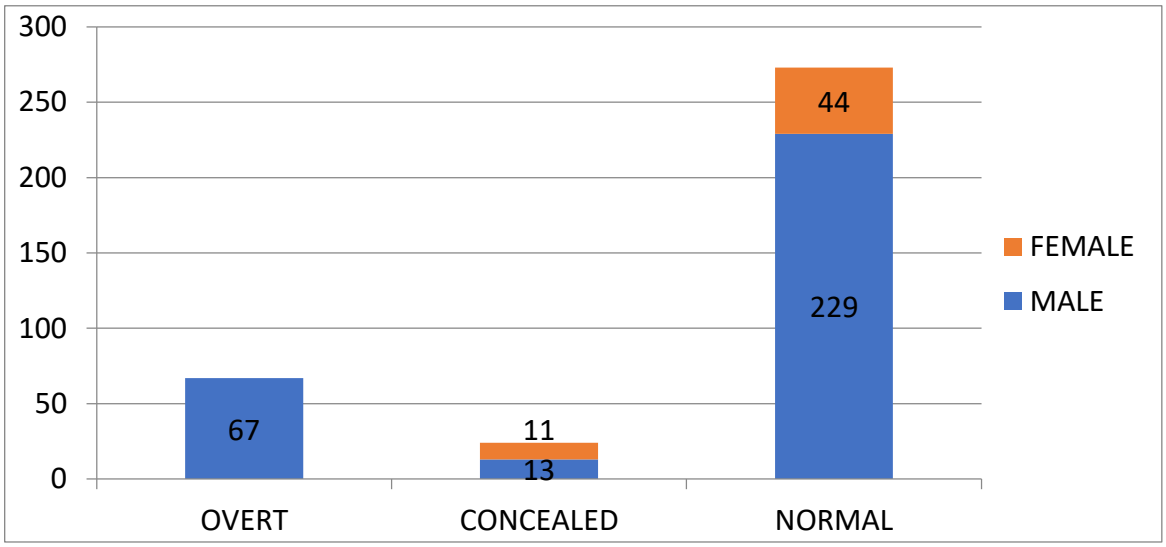
Table : Age and development of renal dysfunction

AGE RANGE	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
41-49 years	0	0	25(100%)	25(100%)	0.001
50-59 years	9(9.2%)	0	89(90.8%)	98(100%)	
60-69 years	58(31.4%)	11(5.9%)	116(62.7%)	185(100%)	
≥70 years	0	13(23.2%)	43(76.8%)	56(100%)	
Total	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

In the age group of 60-69, 31.4% had overt renal dysfunction and 5.9% had concealed renal dysfunction. 9.2% of the patients in the age group of 50-59 had overt variety and 23.2 % in the age group of more than 70 had concealed renal dysfunction. There was a statistically increased prevalence of renal dysfunction with the age>60(p value- 0.001).

Table : Gender and Renal dysfunction

GENDER	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
MALE	67(21.7%)	13(4.2%)	229(74.1%)	309(100%)	
FEMALE	0	11(20%)	44(80.0%)	55(100%)	0.003
TOTAL	67(18.4%)	24(6.6%)	273(75%)	364(100%)	



21.7% the males had overt renal dysfunction, 4.2% of the males and 20% of the females had concealed renal renal dysfunction. There was a statistical significance that female COPD had more chance of developing concealed renal dysfunction(p value – 0.003).

Table : mMRC grading and renal dysfunction

mMRC GRADE	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
1	8(21.6%)	0	29(78.4%)	37(100%)	0.017
2	45(19.8%)	21(9.3%)	161(70.9%)	227(100%)	
3	14(14.0%)	3(3.0%)	83(83%)	100(100%)	
Total	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

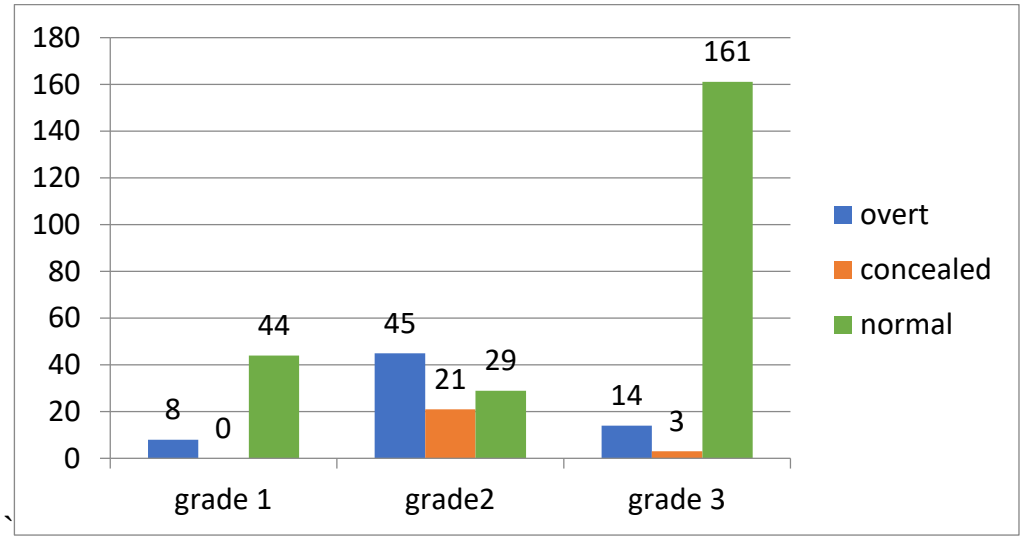


Fig : mMRC grading and Renal dysfunction

21.6% of the patients with grade 1 mMRC developed overt variety, 19.8% and 9.3% of the patients with grade 2 mMRC developed overt and concealed renal failure respectively. 14% and 3% of the patients with grade 3 mMRC developed overt and concealed renal failure respectively. The results were statistically significant(0.017)

Table : CAT Score and Renal dysfunction

CAT SCORE	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
<10	41(19.2%)	10(4.7%)	162(76.1%)	213(100%)	0.214
≥10	26(17.2%)	14(9.3%)	111(73.5%)	151(100%)	
TOTAL	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

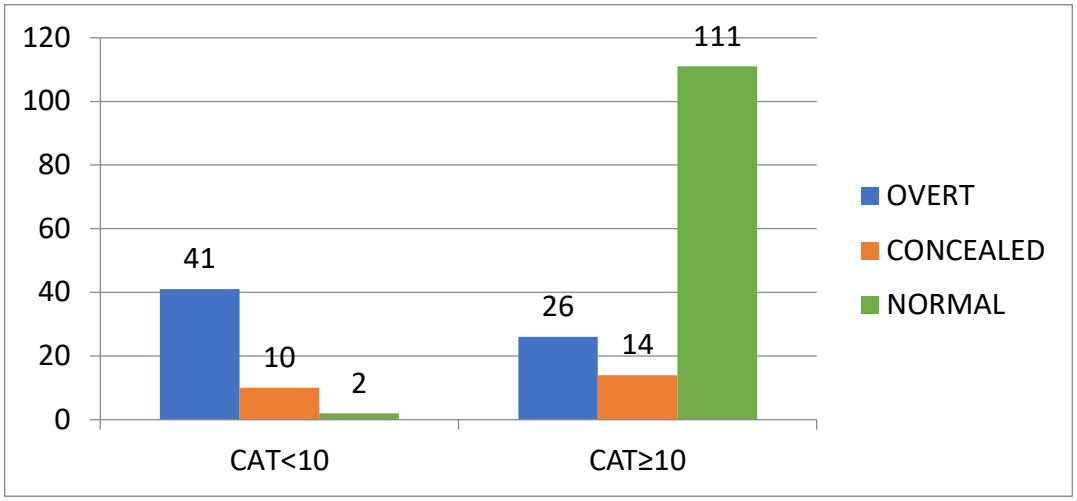


Fig : CAT Score and renal dysfunction

Among the patients with CAT score < 10 19.2% developed overt and 4.7% developed concealed renal dysfunction. Among the patients with CAT score ≥10 17.2% developed overt and 9.3% developed concealed renal dysfunction. There was no statistical significance between CAT Score and development of renal dysfunction.

Table : Previous hospitalisation and renal dysfunction

PREVIOUS HOSPITALISATION	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
0	54(18.1%)	17(5.7%)	228(76.3%)	299(100%)	
≥1	13(20.0%)	7(10.8%)	45(69.2%)	65(100%)	0.047
TOTAL	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

20% and 10.8% of the patients with ≥1 previous hospitalisation developed overt renal dysfunction and concealed renal dysfunction respectively. The results were statistically significant (p value 0.047)

Table : Degree of airflow limitation and Renal dysfunction

FEV1	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
MILD	3(37.5%)	0	5(62.5%)	8(100%)	0.035
MODERATE	23(18.7%)	3(2.4%)	97(78.9%)	123(100%)	
SEVERE	29(15.3%)	21(11.1%)	139(73.5%)	189(100%)	
VERY SEVERE	12(27.3%)	0	32(72.7%)	44(100%)	
Total	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

Fig : Degree of airflow lilitation and renal dysfunction

15.3% and 27.3% of the patients who developed overt renal dysfunction had severe and very sever airflow limitation. 11.1% of the patients who had developed concealed variety had severe airflow limitation.There was a statistically significant increase in renal dysfunction in patients with FEV1 ≤50%(p value- 0.035)

Table : GOLD category and development of renal dysfunction

GOLD CATEGORY	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
CATEGORY A	8 (26.7%)	0	22(73.3%)	30(100%)	0.051
CATEGORY B	46(17.1%)	17(6.3%)	206(76.6%)	269(100%)	
CATEGORY D	13(20.0%)	7(10.8%)	45(69.2%)	65(100%)	
Total	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

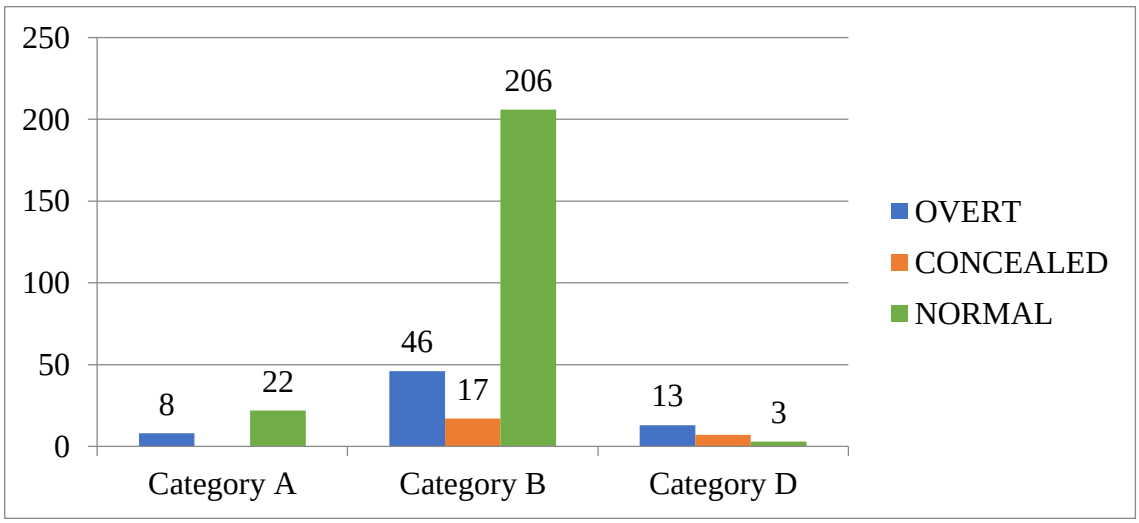


Fig : GOLD Category and development of renal dysfunction

Among the patients with Category B GOLD staging, 17.1% had overt variety and 6.3% had concealed variety. Among Category D 20% had overt and 10.8% had concealed variety. The prevalence of renal dysfunction by GOLD Category is towards statistical significance (p value – 0.051)

Table : Pack years and Renal Dysfunction

PACK YEARS	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL
0	8(6.9%)	14((12.1%)	94(81%)	116
1-20	18(29%)	3(4.8%)	41(66.1%)	62
20-40	13(20%)	0	52(80%)	65
≥40	28(23.1%)	7(5.8%)	86(71.1%)	121
TOTAL	67	24	273	364

Among the concealed renal dysfunction 12.1% were non-smokers, among the Patients with pack years more than 40, 23.1% had overt renal failure and 5.8% had concealed renal dysfunction.

Table : BMI Range and the Renal dysfunction

BMI RANGE	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
<18.5 (UNDER WEIGHT)	5(7.5%)	7(10.4%)	55(82.1%)	67(100%)	0.035
18.5- 24.9 (NORMAL)	53(23.8%)	14(6.3%)	156(70.0%)	223(100%)	
25-29.9 (OVER WEIGHT)	9(12.9%)	3(4.3%)	58(82.9%)	70(100%)	
≥30 (OBESE)	0	0	4(100%)	4(100%)	
Total	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

7.5% and 10.4 % of the underweight patients developed overt and concealed renal failure respectively.23.8% and 6.3% of the normal patients developed overt and concealed renal failure respectively.The results were statistically significant(p value – 0.041).The prevalence were more among patients with BMI< 25.

Table : Anemia and Renal dysfunction

HAEMOGLOBIN VALUES	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
≤10	32(16.5%)	11(5.7%)	151(77.8%)	194	0.025
>10	35(20.6%)	13(7.6%)	122(71.8%)	170	
TOTAL	67	24	273	364	

Renal dysfunction itself can contribute to the development of Anemia.

Among the study population 194 were anemic, among them 16.5% developed overt renal dysfunction and 5.7% developed concealed renal dysfunction.

There was a statistical significance between the development of renal dysfunction and anemia (p value – 0.025)

Table : Diabetes mellitus and Renal dysfunction

DM	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
YES	0	13(27.7%)	34(72.3%)	47(100%)	0.028
NO	67(21.1%)	11(3.5%)	239(75.4%)	317(100%)	
TOTAL	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

27.7% of patients with diabetes developed concealed renal dysfunction.

Table : Systemic hypertension and Renal dysfunction

SHT	OVERT RENAL FAILURE	CONCEALED RENAL FAILURE	NORMAL RENAL FUNCTION	TOTAL	p value
YES	12(19.4%)	9(14.5%)	41(66.1%)	62(100%)	0.038
NO	55(18.2%)	15(5%)	232(76.8%)	302(100%)	
TOTAL	67(18.4%)	24(6.6%)	273(75%)	364(100%)	

19.4% and 14.5% of the patients with SHT developed overt and concealed renal dysfunction respectively.

DISCUSSION

DISCUSSION

This cross sectional study was conducted on 364 Chronic Obstructive Pulmonary Disease patients in Rajiv Gandhi Government General Hospital. This research was done in order to estimate the prevalence of renal dysfunction in Chronic Obstructive Pulmonary Disease patients.

In the present study, the prevalence of renal dysfunction is 25%, among them the prevalence of overt renal failure was 18.4% and prevalence of concealed renal failure was 6.6%. Various studies has been done in India to estimate the prevalence of renal dysfunction among general population. Ajay K Singh et al had done a study called SEEK(Screening and Early Evaluation of Kidney Disease) and found that prevalence of CKD with eGFR< 60 was approximately 6%.

Singh et al had done a study among urban and semi urban delhi population and had found that prevalence of renal failure (eGFR<60) was 6% among urban population and 4.2% among semi urban population. In a study done by Tiwari et al the prevalence was 4%. Hence by comparing with other indian studies the prevalence of renal dysfunction is 4 times higher among COPD when compared with the general population.

Ibrahim l.Elmahallawy et al [52] reported an increased incidence of 46% of renal dysfunction among them prevalence of overt renal failure was 20% and prevalence of concealed renal failure was 26%.

Raffaele Antonelli Incalzi et all [53] reported an incidence of 43% of renal dysfunction among them prevalence of overt renal failure was 22.2% and prevalence of concealed renal failure was 20.8%.

Takayuki Yoshizawa et all [54] found that 31% of the study population developed renal dysfunction.

Sharanya et al [55] reported an incidence of 37% of renal dysfunction among COPD patients.

Bjarte Gjerde et all [56] had a prevalence of 9.6% in Female COPD patients and 5.1% in male COPD patients.

In our study, the prevalence of renal dysfunction in high among the COPD patients when the Age is > 60. In the age group of 60-69, 31.4% had overt renal dysfunction and 5.9% had concealed renal dysfunction and 23.2 % in the age group of more than 70 had concealed renal dysfunction. Among the age group of 40-60 9.2% of the study population had renal dysfunction and all of them had overt renal failure. Ibrahim l.Elmahallawy et al [52] had found that Age was an independent correlate of Overt renal dysfunction with an OR of 3.76 & 95% C.I: 2.26-6.88, it was found that for each 1 year increase in age the risk is 3.76 times.

The patients with concealed renal dysfunction were more frequently in the age group of more than 60 with the average age of 65.5.Raffaele Antonelli Incalzi et all [53] found that the average of prevalence of renal dysfunction was

76.3 for concealed variety and 75.8 for overt variety and had found that most of the patients with concealed variety were in the age group of > 70.

In our study 25.9% of the males had renal dysfunction and 20% of the females had renal dysfunction and all of them had concealed variety. Ibrahim l.Elmahallawy et al [52] had found that the prevalence is more common among males and 70% of the overt renal dysfunction were males and 50% of the concealed renal dysfunction were males and it was statistically significant. Raffaele Antonelli Incalzi et all [53] found that 73% were males in concealed renal dysfunction and 78% were males in the overt renal dysfunction and had no statistical significance.

Based on the FEV1%, the prevalence of renal dysfunction is high when the disease is more severe, i.e, most of the patients with renal dysfunction had either Stage 3 or Stage 4 GOLD COPD severity and similar findings were observed in the study done by Ibrahim l.Elmahallawy et al [52].

Ibrahim l.Elmahallawy et al [52] had found that, most of the patients with both concealed and overt renal dysfunction had either Stage 3 or Stage 4 GOLD COPD severity. The average FEV1 values were 38.5% and 34.72% among the concealed and overt renal dysfunction. Raffaele Antonelli Incalzi et all [53] found that FEV1% was not significantly associated with the development of renal dysfunction among COPD patients.

In our study smoking status was significantly associated with the development the renal dysfunction. Ibrahim l.Elmahallawy et al [52] had found that smoking status was significantly associated with the development of renal dysfunction. The average pack years among the concealed renal dysfunction and overt renal dysfunction were 27 and 32.5.The average pack years in the study done by Raffaele Antonelli Incalzi et all [53] were 40.7 among the concealed renal dysfunction and 50.7 among the overt renal dysfunction.

Since a proportion of patients with COPD has a reduced muscle mass, BMI was evaluated with the prevalence of renal dysfunction. In our study 7.5% and 10.4 % of the underweight patients developed overt and concealed renal failure respectively.23.8% and 6.3% of the normal patients developed overt and concealed renal failure respectively.Ibrahim l.Elmahallawy et al [52] had found that the average BMI in the concealed group was 28.78 and 26.11 in overt variety and it was not statistically significant. Raffaele Antonelli Incalzi et all [53] observed that the average BMI in the concealed group was 26.5 and in the overt variety was 29.2 and it was statistically significant.

Renal dysfunction could be an underlying cause of Anemia in COPD due to impaired erythropoietin production. Ibrahim l.Elmahallawy et al [52] had found that haemoglobin level had no significance in the development of renal dysfunction. Raffaele Antonelli Incalzi et all [53] had found that Haemoglobin status was significantly associated with the development of renal dysfunction. The prevalence of anemia among the concealed renal dysfunction was 23% and in overt renal dysfunction was almost 40%. And the linear relationship was also found after stratification for age and gender.

In our study population Diabetes and Hypertension were significantly associated with the development of renal dysfunction. In our study Prevalence of Renal dysfunction among diabetes and hypertension were 27.7% and 33.9%. The prevalence is higher when compared with the general population. In a study done by Rajesh et al in Haryana the prevalence of renal dysfunction (eGFR < 60) in diabetes mellitus was 16.9%.In a study done by Deidra et al in United States the prevalence of renal dysfunction (eGFR < 60) in Hypertension was 19.6%.

Ibrahim l.Elmahallawy et al [52] had done a backward stepwise logistic regression model and found that the presence of comorbidities like Diabetes and Hypertension were significantly associated with the development of Concealed renal dysfunction.

Raffaele Antonelli Incalzi et all [53] had found that patients with overt renal dysfunction had a higher overall comorbidity and the prevalence of diabetes was higher among them. The odds ratio for diabetic patients developing concealed and overt renal dysfunction was 1.96 and 2.25 respectively. Among the other comorbidity the presence of musculoskeletal disease has increased the risk of developing concealed renal dysfunction by 1.96 times.

In our study the CAT Score and the prevalence of renal dysfunction had no statistical significance. No other studies had shown significant relationship between CAT score and the development of renal dysfunction.

CONCLUSION

CONCLUSION

1. In our study population, 25% of the COPD patients developed renal dysfunction. Among them 18.4% had overt renal failure(e GFR<60, Creatinine>1.2) and 6.6% had concealed renal failure (e GFR<60, Creatinine<1.2).

2. Among the Female COPD patients who had renal dysfunction all the 20% had concealed renal failure.

3. Significant risk factors associated with the development of renal dysfunction in COPD patients are:

    - Age > 60
    - mMMRC grade ≥ 2
    - FEV1% ≤ 50 % (GOLD 3 AND GOLD 4)
    - Smokers with pack years > 40.
    - Associated with Diabetes And Hypertension

4. Even though Diabetes and Hypertension are associated with the development of Renal dysfunction, the prevalence of renal dysfunction is more when they are associated with COPD and the prevalence increases when the severity of COPD is higher (GOLD 3 and 4).

LIMITATIONS

1. This is a hospital based study, extrapolating the results of the study to the general population may not be accurate enough, hence further studies has to be done in the general population.

2.This is a cross sectional study done in a single centre and controls were not included in the study.

3. Glomerular Filtration Rate (GFR) was not measured directly. However CKD EPI creatinine equation is a reliable surrogate for measured GFR in both the healthy elderly and the diseased population.

4.Specific inflammatory markers like C-Reactive Protein, IL-6 and fibrinogen were not seen in the study. The correlation between renal dysfunction and these bio markers would have given a better outcome.

RECOMMENDATIONS

In COPD patients the screening for renal function should not only be estimated by serum creatinine, it should also be done using Estimated Glomerular Filtration Rate calculation, since the muscle mass is decreased in COPD and hence creatinine value may be falsely low.

Since female COPD patients had 20% concealed renal failure, Female COPD patients must be more cautiously screened using Estimated Glomerular Filtration Rate.

BIBILIOGRAPHY

BIBLIOGRAPHY

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859): 2095-128.

2. Global Initiative for Chronic Obstructive Lung Disease GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE UPDATED 2016 Chapter 1

3. Lindberg A, Eriksson B, Larsson LG, Rönmark E, Sandström T, Lundbäck B, et al. Seven-year cumulative incidence of COPD in an age-stratified general population sample. Chest 2006; 129: 879-85.

4. Jindal S. K, Aggarwal AN, Chaudhry K, Chhabra SK, D'Souza GA, Gupta D, et al. Asthma Epidemiology Study Group. A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. Indian J Chest Dis Allied Sci 2006; 48: 23-9.

5. Bjartveit K, Tverdal A. Health consequences of smoking 1-4 cigarettes per day. Tobacco Control. 2005;14:315–20.

6. Vedel-Krogh S1,2,3, Nielsen SF1,2,3, Lange P2,4,5, Vestbo J6, NordestgaardBG1,2,3. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. Am J Respir Crit Care Med. 2016 May 1;193(9):965-74. doi: 10.1164/rccm.201509-1869OC.

7. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: A study of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiology. 2002; 156:738–46.

8. Chhabra SK, Chhabra P, Rajpal S, Gupta RK. Ambient air pollution and chronic respiratory morbidity in Delhi. Arch Environ Health.2001; 56:58

9. Kan H, Heiss G, Rose KM, 37. Whitsel E, Lurmann F, London SJ, et al. Traffic exposure and lung function in adults: the Atherosclerosis Risk in Communities study. Thorax 2007; 62: 873-9.

10. Stoller JK,Aboussuoan LS.Alpha 1-antitrypsin deficiency.Lancet 2005;365(9478): 2225-36.

11. Decramer M, Janssens W, Miravitlles M. Chronic obstructive Pulmonary disease. Lancet 2012; 379: 1341-51

12. Comorbidities of COPD Arnaud Cavaillès, Graziella Brinchault-Rabin, Adrien Dixmier, François Goupil, Christophe Gut-Gobert, Sylvain Marchand-Adam, Jean-Claude Meurice, Hugues Morel, Christine Person-Tacnet, Christophe Leroyer, Patrice DiotEuropean Respiratory Review 2013 22: 454-475; **DOI:**10.1183/09059180.00008612

13. Kim DK, Cho MH, Hersh CP, Lomas DA, Miller BE, Kong X, et al. ECLIPSE, ICGN, and COPDGene Investigators. Genome-wide association analysis of blood biomarkers in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186:1238–47

14. Systemic inflammation in chronic obstructive pulmonary disease EJ.D. Oudijk, JW.J. Lammers, L. Koenderman European Respiratory Journal 2003 22: 5s-13s; **DOI:** 10.1183/09031936.03.00004603a

15. Skyba P, Ukropec J, Pobeha P, Ukropcova B, Joppa P, Kurdiova T, et al. Metabolic phenotype and adipose tissue inflammation in patients with chronic obstructive pulmonary disease. Mediators Inflamm 2010. 2010:173498

16. Systemic inflammation in chronic obstructive pulmonary disease: a population-based study Francisco GarciaRio,Marc Miravitlles,Joan B Soriano,Luis Muñoz,Enric Duran- Tauleria, *Respiratory Research*2010**11**:63 https://doi.org/10.1186/1465-9921-11-63

17. Hurst JR, Wilkinso TM, Perera WR, Donaldson GC, Wedzicha JA. Relationships among bacteria, upper airway, lower airway, and systemic inflammation in COPD. Chest. 2005;127:1219–26.

18. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: A systematic review and a metaanalysis. Thorax. 2004;59:574–80

19. Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations.Thorax 2000; 55: 114–120.

20. Yende S, Waterer GW, Tolley EA, et al. Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. Thorax 2006; 61: 10–16.

21. Janssen SP, Gayan-Ramirez G, Van den BA, et al.Interleukin-6 causes myocardial failure and skeletal muscle atrophy in rats. Circulation 2005; 111: 996–1005.

22. Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor-a levels and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994; 150: 1453–1455.

23. Takabatake N, Nakamura H, Abe S, et al. The relationship between chronic hypoxemia and activation of the tumor necrosis factor-a system in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 1179–1184.

24. Broekhuizen R, Grimble RF, Howell WM, et al. Pulmonary cachexia, systemic inflammatory profile, and the interleukin 1b-511 single nucleotide polymorphism. Am J Clin Nutr 2005; 82: 1059–1064.

25. de Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers RM. Elevated TNF-a production by peripheral blood monocytes of weight-losing COPD patients. Am J Respir Crit Care Med 1996; 153: 633–637.

26. Takabatake N, Nakamura H, Abe S, et al. The relationship between chronic hypoxemia and activation of the tumor necrosis factor-a system in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 1179–1184.

27. Tracey KJ, Wei H, Manogue KR, et al. Cachectin/tumor necrosis factor induces cachexia, anemia and inflammation. J Exp Med 1988; 167: 1211–1227.

28. Spruit MA, Gosselink R, Troosters T, et al. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. Thorax 2003; 58: 752–756.

29. Perera WR, Hurst JR, Wilkinson TM, et al. Inflammatory changes, recovery and recurrence at COPD exacerbation. Eur Respir J 2007; 29: 527–534.

30.Mold C, Rodic-Polic B, Du Clos TW. Protection from Streptococcus pneumoniae infection by C-reactive protein and natural antibody requires complement but not Fcc receptors. J Immunol 2002; 168: 6375–6381.

31.Dahl M, Tybjaerg-Hansen A, Vestbo J, Lange P, Nordestgaard BG. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 164: 1008–1011.

32.He R, Shepard LW, Chen J, Pan ZK, Ye RD. Serum amyloid A is an endogenous ligand that differentially induces IL-12 and IL-23. J Immunol 2006; 177: 4072–4079

33.Sin DD, Leung R, Gan WQ, Man SP. Circulating surfactant protein D as a potential lung-specific biomarker of health outcomes in COPD: a pilot study. BMC Pulm Med 2007; 7: 13.

34 .Grimm RH Jr, Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all-cause mortality. JAMA 1985; 254: 1932–1937.

35. Traves SL, Smith SJ, Barnes PJ, Donnelly LE. Specific CXC but not CC chemokines cause elevated monocyte migration in COPD: a role for CXCR2. J Leukoc Biol 2004; 76:441–450.

36. Aldonyte R, Jansson L, Piitulainen E, Janciauskiene S. Circulating monocytes from healthy individuals and COPD patients. Respir Res 2003; 4: 11.

37. Burnett D, Chamba A, Hill SL, Stockley RA. Neutrophils from subjects with chronic obstructive lung disease show enhanced chemotaxis and extracellular proteolysis.Lancet 1987; 2: 1043–1046.

38. Pons J, Sauleda J, Ferrer JM, et al. Blunted cd T lymphocyte response in chronic obstructive pulmonary disease. Eur Respir J 2005; 25: 441–446.

39. Palange P, Testa U, Huertas A, et al.Circulating haemopoietic and endothelial progenitor cells are decreased in COPD. Eur Respir J 2006; **27**: 529–541

40. Gosker HR, Kubat B, Schaart G, van der Vusse GJ, Wouters EF, Schols AM. Myopathological features in skeletal muscle of patients with chronic obstructive pulmonary disease. Eur Respir J 2003; 22: 280–285

41. Carter JD, Patel S, Sultan FL, et al. The recognition and treatment of vertebral fractures in males with chronic obstructive pulmonary disease. Respir Med 2008; 102: 1165–1172.

42. Anisman H, Merali Z, Hayley S. Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: comorbidity between depression and neurodegenerative disorders. Prog Neurobiol 2008; 85: 1–74.

43. Ben-Zaken CS, Pare PD, Man SF, Sin DD. The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex

differences in cigarette smoke metabolism. Am J Respir Crit Care Med 2007; 176: 113–120.

44. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J. 2008;32:962–9.

45. Jelic S, Padeletti M, Kawut SM, et al. Inflammation,oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation 2008; 117: 2270–2278.

46. Geslain-Biquez C, Vol S, Tichet J, Caradec A, D'Hour A, Balkau B. D.E.S.I.R. study. The metabolic syndrome in smokers. Diabetes Metab.

47. D.Chandra, J.A. Stamm, P.M. Palevsky, et al, The relationship between pulmonary emphysema and kidney function in smokers, Chest 11 (2012) 1456.

48. P.Palange, Renal and hormonal abnormalities in chronic obstructive pulmonary disease (COPD), Thorax 53 (1998) 989–991.

49. S. Satarug, P. Ujjin, Y. Vanavanitkun, et al, Effects of cigarette smoking and exposure to cadmium and lead on phenotypic variability of hepatic CYP2A6 and renal function biomarkers in men, Toxicology 204 (2004) 161–173.

50. M.J. Sevenoaks, R.A. Stockley, Chronic obstructive pulmonary disease, inflammation and co-morbidity—a common inflammatory phenotype?, Respir Res. 7 (2006) 70.

51. J.B. Soriano, G.T. Visick, H. Muellerova, N. Payvandi, A.L. Hansell, Patterns of comorbidities in newly diagnosed COPD and asthma in primary care, Chest 128 (4) (2005) 2099–2107.

52. Ibrahim I. Elmahallawy a,*, Mahmoud A Qora b Egyptian Journal of Chest Diseases and Tuberculosis (2013) 62, 221–227

53. DOI 10.1378/chest.09-1710 *Chest* 2010;137;831-837; Prepublished online November 10, 2009; Investigators Extrapulmonary Consequences of COPD in the Elderly Study Battaglia, Giuseppe Paglino, Vincenzo Bellia and on behalf of the Raffaele Antonelli Incalzi, Andrea Corsonello, Claudio Pedone, Salvatore

54. Takayuki Yoshizawa1,2 Kazuyoshi Okada3 Sachiko Furuichi1,2 International Journal of COPD 2015:10 1283–1289

55. Sharanya et all JMSCR Vol||05||Issue||08||Page 27211-27214||August

56. Bjarte Gjerde a, Per S. Bakke Elsevier Respiratory Medicine (2012) 106, 361e366

ANNEXURES

ABBREVIATIONS

COPD	-	Chronic obstructive pulmonary diseases
CKD	-	Chronic Kidney Disease
CAT	-	COPD assessment test
MMRC	-	Modified medical research council
SNP	-	Single Nucleotide Polymorphism
TNF-α	-	Tumour Necrosis Factor -alpha
BMI	-	Body Mass Index
PHT	-	Pulmonary hypertension
ESR	-	Erythrocyte sedimentation rate
FEV1	-	Forced expiratory volume in one second
FVC	-	Forced vital capacity
DM	-	Diabetes Mellitus
SHT	-	Systemic Pulmonary Hypertension

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"TO ESTIMATE THE PREVALENCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE"** of the candidate **DR.V.ARUNSHANKAR** with registration number **201627001** for the award of MD in the branch of **Tuberculosis & Respiratory diseases.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that uploaded thesis file contains from introduction to conclusion pages and result shows **3 percentage** of plagiarism in the dissertation.

Guide & Supervisor sign with seal

URKUND

Urkund Analysis Result

Analysed Document:	THESIS FINAL.docx (D42403269)
Submitted:	10/11/2018 7:27:00 AM
Submitted By:	shankarv.dr@gmail.com
Significance:	3 %

Sources included in the report:

https://helda.helsinki.fi/handle/10138/36152
https://www.duo.uio.no/handle/10852/49217
https://www.researchgate.net/publication/273508866_Prevalence_of_chronic_renal_failure_in_COPD_patients
https://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease

Instances where selected sources appear:

10

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.Arunshankar.V.
PG in MD TBCD
Institute of Thoracic Medicine/
Madras Medical College
Chennai 600 003

Dear Dr.Arunshankar.V,

The Institutional Ethics Committee has considered your request and approved your study titled **"TO ESTIMATE THE PREVALANCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE" - NO.15052017**

The following members of Ethics Committee were present in the meeting hold on **02.05.2017** conducted at Madras Medical College, Chennai 3

1.Prof.Dr.C.Rajendran, MD.,	:Chairperson
2.Prof.R.Narayana Babu, MD.,DCH.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	:Member Secretary
4.Prof.S.Suresh,MS.,Prof.of Surgery,MMC, Ch-3	: Member
5.Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
6.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
7.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
8.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

EVALUATION FORM

Name: Age: Sex:

OP/Ip number: Duration of illness:

Smoking history:

mMRC Grade:

CAT score:

Previous exacerbations and
Hospital admission:

Co-morbidity:

Blood investigations:

RBS: urea- creatinine- Na- K-

Sr.Albumin: Hb-

eGFR:

Chest xray :

SPIROMETRY:
FEV1:
FVC:
% FEV1/ FVC:

Height:

Weight:

SpO2:

USG Abdomen:

PATIENT CONSENTFORM

Study Detail : **" TO ESTIMATE THE PREVALANCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE "** Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Identification Number:

Patient may check (√) these boxes :a) I confirm that I have understood the purpose of procedure for above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

b) I understand that my participation in study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

e) I hereby consent to participate in this study. ❑

f) I hereby give permission to undergo detailed clinical examination, Radiographs ,blood investigations and other procedures as required. ❑

Signature/thumb impression of patients/patients attendar

Signature of Investigator:

Patient's Name and Address:

Study Investigator's Name: **Dr.Arunshankar V**

PATIENT INFORMATION SHEET

TITLE OF THE STUDY: **" TO ESTIMATE THE PREVALANCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE "** We are conducting a study among patients admitted in Rajiv Gandhi Government General Hospital, Chennai-600003.

The purpose of this study is the **" TO ESTIMATE THE PREVALANCE OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE "**

1.We are selecting cases based on the inclusion criteria of the study .

2.Selected patients will undergo basic blood investigations,sputum examination, CXR,spirometry, arterial blood gas analysis, urine analysis, USG abdomen, Renal Doppler based on a study protocol to arrive at a diagnosis and to subsequently treat the patient.

3.The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

4.Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

5.The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator
Date :

Signature of Participant

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராயச்சியின் தலைப்பு

நாள்பட்ட மூச்சுக்குழாய் அடைப்பு நோய் உள்ளவர்களில், சிறுநீரக செயற்பாட்டின்மையை கண்டறியும் ஆராய்ச்சி

ஆய்வு நிலையம் : நெஞ்சக நோய் மருத்துவத் துறை,
சென்னை மருத்துவக் கல்லூரி சென்னை – 3.

பங்கு பெறுவரின் பெயர் :
பங்குபெறுபவரின் எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் 'இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு

நாள்பட்ட மூச்சுக்குழாய் அடைப்பு நோய் உள்ளவர்களில், சிறுநீரக செயற்பாட்டின்மையை கண்டறியும் ஆராய்ச்சி

ஆய்வாளர் பெயர் ; மரு.வே.அருண்சங்கர்
ஆய்வு நிலையம் : நெஞ்சக நோய் மருத்துவத் துறை,
சென்னை மருத்துவக் கல்லூரி சென்னை - 3.

இந்த ஆய்வில் தங்களை பங்கேற்க அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆராய்ச்சியில் பங்கேற்கலாமா வேண்டாமா என்பதை முடிவு செய்ய உதவியாக இருக்கும். இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை நீங்கள் தயங்காமல் கேட்கலாம்.

இந்த ஆராய்ச்சியில் நாள்பட்ட மூச்சுக்குழாய் அடைப்பு நோய் உள்ளவர்களில், சிறுநீரக செயற்பாட்டின்மையை கண்டறிய இரத்தப்பரிசோதனை, சளி பரிசோதனை மற்றும் சிறுநீர் பரிசோதனை செய்யப்படும். USG Abdomen and Renal Doppler எனப்படும் ஸ்கேன் செய்யப்படும். அதற்கு தங்கள் ஒத்துழைப்பு தேவை

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்கு ஏற்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறேம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

---------- ----------

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்
தேதி

S.NO	AGE	GENDER	Mmrc grade	CAT	PREVIOUS HOSPITALISATION	FEV1	FEV1%	SEVERITY	CATEGORY	PACK YEARS	BMI	DM	HT	CAD	UREA	CREATININE	eGFR	RBS	Hb	T.B	D.B
1	63	M	2	6	0	1.31	76	2	B	80	21.36	NO	NO	NO	31	0.5	115	137	12.6	0.6	0.3
2	50	F	2	8	0	1.16	40	3	B	0	22.29	YES	YES	NO	17	0.7	101	133	12.2	0.6	0.2
3	70	M	2	6	0	1.64	65	2	B	0	22.83	NO	YES	NO	37	1	76	112	13.6	0.7	0.5
4	60	M	3	7	0	1.73	66	2	B	0	33.77	NO	NO	YES	20	1.2	65	198	15.3	0.5	0.3
5	75	M	2	11	1	1.51	49	3	D	54	17.57	NO	NO	NO	19	1.2	59	159	12.3	0.3	0.2
6	60	M	2	8	0	1.14	45	3	B	10	23.43	NO	NO	NO	29	1.4	54	118	15.6	0.7	0.4
7	69	M	2	12	0	1.71	82	1	B	50	23.43	NO	NO	YES	31	1.3	56	97	14.2	0.3	0.2
8	60	M	1	6	0	1.66	58	2	A	15	23.68	NO	NO	NO	15	0.5	118	100	13.4	0.4	0.3
9	61	M	2	8	0	0.58	31	3	B	80	17.28	NO	NO	NO	15	0.7	102	130	12.8	0.8	0.3
10	75	M	2	12	0	1.04	62	2	B	0	25.19	NO	NO	NO	17	1.2	58	70	13.1	1.4	0.7
11	63	F	2	14	0	0.53	33	3	B	0	23.68	NO	NO	NO	29	1.2	64	96	11.9	0.8	0.6
12	53	M	3	8	0	1.28	45	3	B	34	24.29	NO	NO	NO	17	1.2	69	75	12.9	0.7	0.3
13	55	M	2	10	0	0.49	24	4	B	44	18.51	NO	NO	NO	20	0.6	113	128	13.6	0.6	0.3
14	65	M	2	7	0	0.76	25	4	B	13	28.75	NO	NO	NO	25	0.5	114	123	11.4	0.4	0.3
15	61	M	2	9	0	0.95	43	3	B	46	24.27	NO	NO	NO	35	1.3	59	88	15.5	1.2	0.6
16	70	M	2	6	0	0.83	37	3	B	52	15.62	NO	NO	NO	22	0.6	102	118	12.6	0.3	0.1
17	60	M	2	12	0	1.05	62	2	B	17	18.75	NO	NO	NO	55	1.4	54	63	13.3	0.6	0.4
18	67	F	2	11	0	0.65	32	3	B	0	30.46	NO	NO	NO	31	0.9	66	116	11.8	0.4	0.2
19	58	F	2	10	0	0.57	35	3	B	0	22.38	NO	NO	NO	37	0.8	81	90	11.9	0.7	0.4
20	65	M	3	8	0	1.49	47	3	B	30	23.43	NO	NO	NO	22	1.4	52	104	13.4	1.8	0.9
21	66	M	3	8	0	0.61	33	3	B	82	15.49	NO	NO	NO	26	0.8	93	73	11.2	0.6	0.1
22	53	M	2	6	0	0.95	42	3	B	0	20.88	NO	YES	NO	20	0.8	102	81	12.7	0.8	0.3
23	70	F	3	11	0	0.49	34	3	B	0	24.15	NO	NO	NO	25	0.5	98	102	14.7	0.8	0.5
24	65	M	2	14	1	1.17	60	2	D	0	29.76	NO	YES	NO	24	0.9	89	121	15.1	0.7	0.6
25	55	F	2	6	0	0.63	55	2	B	0	19.6	YES	NO	NO	27	0.6	103	90	10.8	0.7	0.4
26	60	M	3	14	0	0.85	42	3	B	0	28.11	NO	NO	NO	26	0.7	103	70	15.3	1.3	1
27	52	M	2	8	0	0.69	28	4	B	63	19.48	YES	NO	NO	29	0.7	109	228	16.3	0.5	0.4
28	54	M	2	7	0	1.53	34	3	B	34	20.76	YES	YES	NO	25	1.2	68	314	14.2	0.4	0.2
29	64	F	3	11	0	0.74	44	3	B	0	24.8	NO	NO	NO	24	0.9	68	104	10	0.9	0.6
30	78	M	3	16	1	0.57	37	3	D	52	15.26	NO	NO	NO	31	0.9	82	216	11.2	0.2	0.1
31	60	F	2	9	0	0.51	27	4	B	0	17.31	NO	NO	NO	28	0.6	99	98	10.8	0.7	0.4
32	64	M	2	8	0	1.61	63	2	B	38	29.82	NO	NO	NO	34	1.4	53	134	11.4	0.7	0.6
33	65	M	2	14	1	0.57	42	3	D	87	24.61	NO	NO	NO	36	1.3	57	132	12.6	0.8	0.4
34	58	M	2	16	0	2.2	72	2	B	19	18.3	NO	NO	NO	28	1.2	66	97	14.6	0.3	0.2
35	49	M	2	8	0	1.71	47	3	B	53	20.31	NO	NO	NO	17	1	88	102	15.8	0.7	0.3
36	65	M	3	22	0	1.58	46	3	B	90	20.76	NO	YES	NO	54	2	34	85	12.7	1.2	0.7
37	51	F	2	10	1	0.82	37	3	D	96	23.29	NO	NO	NO	20	0.7	96	114	11.1	0.6	0.5
38	54	M	3	16	1	1.97	55	2	D	34	17.54	NO	NO	NO	33	0.8	101	132	17.3	0.5	0.3
39	48	M	2	8	1	1.84	52	2	D	42	23.24	NO	NO	NO	21	0.8	106	91	11	0.5	0.2
40	62	M	3	6	0	0.74	38	3	B	16	21.32	NO	NO	NO	34	0.8	96	122	11.8	0.6	0.3
41	65	M	1	6	0	1.35	62	2	A	63	24.15	NO	NO	NO	35	0.4	125	136	11.9	0.3	0.2
42	52	M	3	8	1	0.94	33	3	D	74	19.53	NO	NO	NO	30	0.7	109	106	11.6	0.5	0.4
43	54	M	2	9	0	0.4	24	4	B	34	19.75	NO	YES	NO	22	0.6	114	148	12.8	0.5	0.3
44	53	M	2	6	0	1.51	77	2	B	82	28.27	YES	NO	NO	20	0.6	115	143	11.9	0.5	0.4
45	82	M	3	14	0	0.54	43	3	B	18	27.08	YES	YES	NO	39	1.2	56	112	12.2	0.6	0.4
46	70	M	2	22	0	1.04	65	2	B	0	23.41	YES	YES	NO	22	1	76	206	11	0.4	0.3
47	60	M	2	18	0	2.21	82	1	B	43	18.47	NO	NO	NO	31	1	81	144	10.6	0.7	0.4
48	70	M	2	16	0	0.85	36	3	B	0	21.27	NO	NO	NO	33	1	76	105	12.2	0.8	0.4
49	72	M	2	14	0	0.83	44	3	B	48	17.56	NO	NO	NO	35	0.9	85	168	11.2	0.5	0.3
50	65	F	2	12	0	1.44	46	3	B	0	22.67	YES	YES	NO	35	1.1	53	214	12.3	0.3	0.1

51	59	M	1	8	0	0.63	28	4	B	94	17.44	NO	NO	NO	23	0.5	119	82	9.6	0.7	0.4
52	71	M	3	12	0	0.74	37	3	B	0	21.37	NO	YES	NO	22	0.6	101	98	11.6	0.5	0.3
53	52	M	2	6	0	0.94	42	3	B	22	20.88	NO	NO	NO	23	0.8	103	94	10.4	0.6	0.3
54	50	M	2	6	0	1.21	57	2	B	0	22.64	NO	YES	NO	32	1.5	54	91	13.8	1.3	0.8
55	62	M	3	14	1	0.52	22	4	D	0	27.91	NO	NO	NO	35	1.1	72	151	12.6	0.5	0.3
56	63	F	2	12	0	1.73	62	2	B	0	27.21	NO	YES	NO	30	0.7	92	178	14.8	0.8	0.4
57	66	F	2	12	0	0.63	33	3	B	0	22.08	NO	NO	NO	32	0.7	90	72	11.1	0.5	0.3
58	52	M	3	6	0	1.37	43	3	B	33	19.84	NO	NO	NO	20	1.2	69	90	15.3	0.8	0.5
59	67	M	2	10	0	1.29	59	2	B	62	21.64	NO	NO	NO	38	1.5	47	138	13	0.6	0.3
60	61	F	2	12	0	1.12	59	2	B	0	28.72	NO	NO	NO	28	0.6	98	164	13.4	0.7	0.5
61	42	M	3	6	0	1.1	52	2	B	32	25.91	NO	NO	NO	30	0.7	116	90	12.5	0.5	0.3
62	60	M	1	7	0	0.58	21	4	A	14	21.91	NO	NO	NO	42	1.4	54	84	11.8	0.4	0.2
63	61	M	2	14	0	1.27	43	3	B	20	17.77	NO	NO	NO	31	1.2	65	100	13.6	0.4	0.2
64	70	M	3	18	0	1.38	32	3	B	9	18.17	NO	NO	NO	17	0.9	86	88	13.3	0.5	0.2
65	61	M	3	12	1	0.71	23	4	D	18	21.48	YES	YES	NO	22	0.8	96	91	12.8	0.8	0.6
66	60	M	2	8	1	0.66	28	4	D	68	16.33	NO	NO	NO	34	1.8	40	177	11.6	0.9	0.5
67	60	M	2	9	0	1.54	67	2	B	61	19.62	NO	NO	NO	17	1	81	89	14.6	0.7	0.4
68	46	M	3	6	0	1.72	64	2	B	0	27.34	NO	NO	NO	15	1.1	80	253	12.3	1.2	0.6
69	64	M	2	10	0	2.06	58	2	B	37	21.27	NO	NO	NO	22	0.8	94	156	13.8	0.5	0.2
70	68	M	2	18	1	1.47	58	2	D	23	27.36	NO	NO	NO	17	1.1	69	52	14.3	0.5	0.4
71	58	M	2	6	0	2.22	72	2	B	38	16.94	NO	NO	NO	16	1.2	66	71	14.4	0.7	0.3
72	60	M	2	8	0	1.19	58	2	B	42	19.38	YES	NO	NO	14	1.1	73	110	13.6	0.4	0.2
73	61	M	2	9	1	0.71	32	3	D	17	22.08	NO	NO	NO	17	1	81	78	12.7	0.9	0.5
74	63	M	2	6	0	1.74	71	2	B	39	24.24	NO	NO	YES	19	1.2	64	73	12.6	0.8	0.4
75	69	M	2	12	0	0.91	41	3	B	7	25.73	YES	NO	NO	26	1.2	61	178	11.2	0.8	0.4
76	58	M	2	6	0	1.61	71	2	B	44	25.77	NO	NO	YES	18	1.2	66	103	12.8	0.4	0.1
77	70	M	2	21	0	0.79	48	3	B	48	18.66	NO	NO	NO	17	0.9	86	171	13.7	0.4	0.2
78	57	M	1	6	0	1.21	37	3	A	0	14.18	NO	NO	NO	20	0.9	94	125	14.2	0.7	0.4
79	55	M	1	8	0	1.72	62	2	A	15	17.5	NO	NO	NO	20	0.8	101	85	13.3	0.5	0.3
80	63	M	1	11	0	1.11	52	2	A	52	20.57	NO	NO	NO	18	0.7	100	182	13.4	0.6	0.4
81	66	M	3	18	1	0.68	31	3	D	17	27.34	NO	NO	NO	25	1	78	161	14.2	0.5	0.3
82	45	M	2	6	0	3.39	83	1	B	23	22.49	YES	YES	NO	18	1	90	222	15.7	0.7	0.3
83	59	M	1	6	0	2.19	81	1	A	0	27.17	NO	NO	NO	26	1.2	66	129	12.4	0.6	0.3
84	70	M	3	8	0	0.97	42	3	B	45	19.65	NO	NO	NO	22	1	76	96	12.8	0.5	0.1
85	58	M	2	12	0	0.88	27	4	B	62	26.34	NO	NO	NO	30	0.8	102	156	12	0.6	0.4
86	44	M	2	6	0	0.96	31	3	B	9	14.03	NO	NO	NO	28	0.7	115	72	11	0.5	0.3
87	63	M	3	11	0	1.61	65	2	B	36	29.82	NO	NO	NO	35	1.4	54	142	11.4	0.7	0.6
88	66	M	2	12	1	0.57	47	3	D	84	24.61	NO	NO	NO	37	1.3	56	138	12.6	0.7	0.4
89	61	M	1	8	0	0.58	23	4	A	17	21.91	NO	NO	NO	40	1.4	55	94	11.8	0.5	90
90	63	M	2	12	0	1.33	45	3	B	20	17.77	NO	NO	NO	33	1.2	64	103	13.6	0.4	0.3
91	51	M	2	8	0	1.23	58	2	B	0	22.64	NO	YES	NO	33	1.5	55	91	13.8	1.3	0.8
92	61	M	3	9	1	0.55	24	4	D	0	27.91	NO	NO	NO	40	1.1	73	151	12.1	0.5	0.3
93	71	M	3	12	0	0.82	38	3	B	0	21.37	NO	YES	NO	24	0.6	102	87	13.1	0.5	0.3
94	53	M	2	8	0	0.94	45	3	B	22	21.32	NO	NO	NO	27	0.8	104	94	11.1	0.6	0.3
95	75	M	2	6	1	1.48	47	3	D	54	17.57	NO	NO	NO	22	1.2	58	163	12.3	0.5	0.2
96	62	M	2	7	0	1.14	46	3	B	10	23.43	NO	NO	NO	29	1.4	53	118	14.9	0.7	0.4
97	65	F	2	9	0	1.47	47	3	B	0	22.67	YES	YES	NO	37	1.1	53	214	12.7	0.5	0.1
98	58	M	1	6	0	0.94	33	3	B	94	17.44	NO	NO	NO	23	0.5	117	82	9.6	0.7	0.4
99	67	F	2	8	0	1.53	48	3	B	0	22.67	YES	NO	NO	36	1.1	52	198	12.8	0.3	0.2
100	71	M	3	9	0	0.85	37	3	B	0	21.27	NO	NO	NO	33	1.1	74	115	12.6	0.7	0.4
101	65	M	2	<10	0	1.41	77	2	B	80	22.32	NO	NO	NO	41	0.6	112	138	13.1	0.5	0.3
102	61	M	3	12	0	0.81	38	3	B	16	20.32	NO	NO	NO	38	0.8	97	132	12.2	0.5	0.3
103	65	M	1	6	0	1.35	63	2	A	63	23.25	NO	NO	NO	36	0.5	123	136	12.5	0.4	0.2
104	54	M	3	14	1	1.12	45	3	D	75	19.53	NO	NO	NO	30	0.8	105	106	11.9	0.5	0.3

105	54	M	2	12	0	0.4	24	4	B	34	19.75	NO	YES	NO	22	0.6	114	148	12.8	0.5	0.3
106	50	M	2	8	0	1.57	76	2	B	82	27.12	YES	NO	NO	20	0.6	118	152	11.9	0.7	0.4
107	82	M	3	22	0	0.73	47	3	B	18	15.32	YES	YES	NO	44	1.2	56	112	12.8	0.6	0.4
108	72	M	2	6	0	1.12	68	2	B	0	23.41	NO	YES	NO	22	1.1	74	212	11.5	0.4	0.2
109	66	M	2	9	0	1.94	74	2	B	43	17.98	NO	NO	NO	31	1	79	144	11.3	0.7	0.4
110	70	M	2	12	0	0.93	38	3	B	0	21.98	NO	NO	NO	33	0.9	78	113	12.2	0.7	0.4
111	73	M	2	16	0	0.89	45	3	B	46	20.21	NO	NO	NO	35	0.9	83	157	11.2	0.9	0.5
112	65	F	2	22	0	1.37	44	3	B	0	21.57	YES	NO	NO	43	1.1	53	164	12.3	0.4	0.1
113	58	M	1	16	0	1.12	41	3	B	93	19.32	NO	NO	NO	32	0.6	118	78	9.8	0.7	0.4
114	71	M	3	12	0	0.74	37	3	B	0	22.65	NO	YES	NO	25	0.6	101	78	11.9	0.6	0.3
115	54	M	2	10	0	0.97	44	3	B	24	20.88	NO	NO	NO	27	0.8	102	94	10.4	0.7	0.3
116	52	M	2	12	0	1.21	58	2	B	0	23.98	NO	YES	NO	32	1.5	53	98	13.4	1.3	0.8
117	62	M	3	14	1	0.87	31	3	D	0	24.89	NO	NO	NO	35	1.1	72	151	12.7	0.5	0.3
118	64	F	2	6	0	1.77	68	2	B	0	23.67	NO	YES	NO	27	0.8	91	188	14.8	0.8	0.5
119	66	F	2	8	0	0.78	37	3	B	0	21.98	NO	NO	NO	32	0.8	90	86	11.1	0.6	0.3
120	52	M	3	9	0	1.39	44	3	B	33	20.76	NO	NO	NO	22	1.2	69	87	15.3	0.8	0.5
121	68	M	2	11	0	1.32	62	2	B	65	24.32	NO	NO	NO	34	1.5	47	144	13.2	0.6	0.2
122	62	F	2	7	0	1.18	62	2	B	0	27.92	NO	NO	NO	32	0.7	97	154	13.4	0.7	0.5
123	63	M	1	8	0	1.21	56	2	A	53	21.89	NO	NO	NO	22	0.6	102	178	13.7	0.6	0.4
124	65	M	3	16	1	0.71	31	3	D	19	27.34	NO	NO	NO	27	1.1	76	161	14.5	0.5	0.3
125	47	M	2	9	0	2.98	77	2	B	27	22.49	YES	YES	NO	18	1	88	198	15.7	0.8	0.3
126	59	M	1	6	0	2.08	77	2	A	0	26.76	NO	NO	NO	28	1.2	66	129	12.4	0.6	0.3
127	68	M	3	8	0	0.89	38	3	B	46	20.12	NO	NO	NO	22	1	77	96	12.8	0.5	0.1
128	58	M	2	9	0	1.12	34	3	B	63	25.98	NO	NO	NO	33	0.9	101	163	12.2	0.6	0.4
129	45	M	2	10	0	0.96	32	3	B	8	15.32	NO	NO	NO	27	0.8	113	87	11.3	0.5	0.3
130	65	M	3	7	0	1.58	63	2	B	37	29.31	NO	NO	NO	36	1.4	53	164	11.4	0.7	0.6
131	66	M	2	12	1	0.82	48	3	D	83	23.21	NO	NO	NO	39	1.3	56	143	12.7	0.7	0.4
132	61	M	1	8	0	0.62	26	4	A	18	21.91	NO	NO	NO	38	1.4	55	89	11.8	0.5	90
133	65	M	2	6	0	1.28	44	3	B	22	17.77	NO	NO	NO	32	1.2	65	103	13.6	0.4	0.3
134	51	M	2	9	0	1.33	62	2	B	0	21.98	NO	YES	NO	35	1.5	54	98	13.8	1.3	0.8
135	60	M	3	14	1	0.76	28	4	D	0	28.12	NO	NO	NO	42	1.1	72	143	12.1	0.5	0.3
136	72	M	3	8	0	0.91	39	3	B	0	20.78	NO	YES	NO	27	0.7	101	87	13.1	0.5	0.3
137	53	M	2	6	0	0.98	47	3	B	24	20.78	NO	NO	NO	28	0.8	103	85	11.8	0.6	0.3
138	76	M	2	18	1	1.54	48	3	D	55	18.32	NO	NO	NO	25	1.2	57	156	12.3	0.6	0.2
139	63	M	2	6	0	1.24	48	3	B	9	22.67	NO	NO	NO	32	1.4	52	118	14.7	0.7	0.4
140	66	F	2	9	0	1.41	46	3	B	0	22.54	NO	YES	NO	39	1.1	52	167	13.1	0.5	0.1
141	58	M	1	8	0	0.91	34	3	B	89	18.12	NO	NO	NO	23	0.6	115	76	9.9	0.7	0.4
142	68	F	2	6	0	1.49	48	3	B	0	22.32	YES	NO	NO	38	1.1	51	165	12.8	0.3	0.2
143	70	M	3	7	0	0.89	38	3	B	0	20.57	NO	NO	NO	35	1.1	75	115	12.8	0.7	0.4
144	64	M	2	8	0	1.33	76	2	B	83	21.36	NO	NO	NO	33	0.6	113	137	12.8	0.6	0.3
145	51	F	2	10	0	1.21	42	3	B	0	21.89	YES	YES	NO	21	0.6	103	124	12.8	0.6	0.2
146	68	M	2	12	0	1.69	67	2	B	0	22.12	NO	YES	NO	38	1	77	121	13.6	0.7	0.5
147	62	M	3	9	0	1.68	64	2	B	0	31.21	NO	NO	YES	22	1.2	64	178	14.9	0.5	0.3
148	76	M	2	16	1	1.44	45	3	D	57	18.12	NO	NO	NO	18	1.2	58	145	12.3	0.4	0.2
149	60	M	2	8	0	1.18	46	3	B	8	22.89	NO	NO	NO	27	1.4	53	116	15.1	0.8	0.4
150	68	M	2	10	0	1.69	82	1	B	52	22.49	NO	NO	YES	33	1.3	55	97	14.2	0.3	0.2
151	59	M	1	6	0	1.71	61	2	A	17	23.54	NO	NO	NO	17	0.6	116	98	13.1	0.4	0.3
152	62	M	2	8	0	0.87	42	3	B	77	19.12	NO	NO	NO	19	0.8	101	122	11.9	0.8	0.3
153	74	M	2	9	0	1.12	64	2	B	0	24.65	NO	NO	NO	22	1.2	57	80	13.4	1.4	0.7
154	65	F	2	7	0	0.78	42	3	B	0	22.79	NO	NO	NO	32	1.2	63	78	11.9	0.8	0.6
155	55	M	3	8	0	1.32	47	3	B	37	23.87	NO	NO	NO	32	1.2	68	75	13.1	0.7	0.3
156	55	M	2	10	0	0.53	26	4	B	44	18.64	NO	NO	NO	22	0.6	113	128	13.6	0.6	0.3
157	64	M	2	9	0	0.84	27	4	B	17	27.74	NO	NO	NO	27	0.6	112	132	11.8	0.4	0.3
158	62	M	2	6	0	1.08	47	3	B	44	23.78	NO	NO	NO	36	1.3	58	88	15.5	1.2	0.6

159	70	M	2	8	0	0.91	38	3	B	51	16.34	NO	NO	NO	25	0.5	103	118	13.1	0.4	0.1
160	61	M	2	9	0	1.12	64	2	B	19	18.32	NO	NO	NO	54	1.4	53	78	13.1	0.7	0.4
161	68	F	2	12	0	0.78	37	3	B	0	28.78	NO	NO	NO	32	0.9	65	122	12.1	0.5	0.2
162	57	F	2	11	0	0.68	42	3	B	0	21.65	NO	NO	NO	36	0.7	83	94	11.9	0.7	0.4
163	64	M	3	6	0	1.51	48	3	B	29	22.17	NO	NO	NO	23	1.4	51	104	13.4	1.8	0.9
164	62	F	2	14	0	1.22	61	2	B	0	27.87	NO	NO	NO	32	0.7	96	144	13.7	0.7	0.5
165	43	M	3	7	0	1.22	53	2	B	33	24.98	NO	NO	NO	32	0.7	117	87	12.9	0.5	0.3
166	60	M	1	8	0	0.63	24	4	A	17	22.65	NO	NO	NO	43	1.4	53	97	11.8	0.4	0.2
167	62	M	2	10	0	1.31	44	3	B	22	18.12	NO	NO	NO	32	1.2	64	96	13.4	0.4	0.2
168	71	M	3	9	0	1.41	37	3	B	9	19.98	NO	NO	NO	21	0.9	85	78	13.1	0.5	0.3
169	61	M	3	7	1	0.78	26	4	D	17	22.15	YES	YES	NO	23	0.7	98	88	12.8	0.8	0.6
170	60	M	2	8	1	0.72	28	4	D	65	17.56	NO	NO	NO	34	1.7	41	177	11.6	0.9	0.5
171	61	M	2	9	0	1.61	71	2	B	63	21.08	NO	NO	NO	19	1.1	79	89	14.3	0.7	0.4
172	46	M	3	14	0	1.84	66	2	B	0	26.73	NO	NO	NO	16	1.1	81	234	12.7	1.2	0.6
173	64	M	2	18	0	2.12	61	2	B	39	22.56	NO	NO	NO	23	0.9	92	148	13.9	0.5	0.2
174	67	M	2	9	1	1.52	59	2	D	21	26.84	NO	NO	NO	18	1.1	68	64	14.4	0.6	0.4
175	59	M	2	10	0	2.12	71	2	B	37	17.45	NO	NO	NO	17	1.2	65	84	14.1	0.6	0.3
176	61	M	2	12	0	1.21	59	2	B	43	20.32	YES	NO	NO	15	1.1	74	110	13.4	0.4	0.2
177	62	M	2	24	1	0.83	34	3	D	19	23.14	NO	NO	NO	18	1.1	79	85	13.4	0.9	0.5
178	63	M	2	6	0	1.82	72	2	B	38	25.02	NO	NO	YES	21	1.2	64	81	12.9	0.7	0.4
179	72	M	2	10	0	1.02	47	3	B	9	25.83	YES	NO	NO	27	1.2	60	165	11.9	0.8	0.4
180	58	M	2	9	0	1.71	74	2	B	45	25.77	NO	NO	YES	21	1.2	65	124	12.8	0.4	0.1
181	70	M	2	8	0	0.92	48	3	B	48	19.22	NO	NO	NO	19	0.9	87	161	13.7	0.4	0.2
182	58	M	1	6	0	1.34	42	3	A	0	15.38	NO	NO	NO	22	0.9	95	144	14.2	0.6	0.4
183	54	M	1	8	0	1.83	64	2	A	17	18.3	NO	NO	NO	21	0.9	100	85	13.3	0.5	0.3
184	63	M	1	6	0	1.24	54	2	A	55	21.12	NO	NO	NO	19	0.8	98	174	14.2	0.7	0.4
185	65	M	3	10	0	1.64	49	3	B	31	23.43	NO	NO	NO	23	1.4	52	112	14.2	1.8	0.9
186	67	M	3	8	0	0.74	36	3	B	85	16.49	NO	NO	NO	27	0.9	92	75	11.2	0.8	0.3
187	54	M	2	6	0	1.12	47	3	B	0	21.32	NO	YES	NO	21	0.8	101	81	12.7	0.8	0.3
188	71	F	3	7	0	0.57	36	3	B	0	23.87	NO	NO	NO	25	0.6	97	112	14.3	0.7	0.5
189	65	M	2	12	1	1.24	62	2	D	0	29.76	NO	YES	NO	25	0.9	89	117	15.3	0.7	0.6
190	56	F	2	9	0	0.85	57	2	B	0	19.68	YES	NO	NO	29	0.6	104	90	11.1	0.7	0.4
191	60	M	3	14	0	0.92	42	3	B	0	28.11	NO	NO	NO	27	0.7	105	74	15.3	1.3	1
192	52	M	2	7	0	0.72	28	4	B	64	19.48	YES	NO	NO	29	0.6	110	198	16.3	0.5	0.4
193	54	M	2	6	0	1.53	36	3	B	31	20.76	YES	YES	NO	26	1.2	67	268	14.8	0.4	0.2
194	66	F	3	9	0	0.88	45	3	B	0	24.89	NO	NO	NO	24	1	65	104	10.4	0.9	0.6
195	77	M	3	11	1	0.64	37	3	D	52	15.26	NO	NO	NO	33	0.9	83	216	11.2	0.2	0.1
196	59	F	2	12	0	0.61	27	4	B	0	18.12	NO	NO	NO	28	0.6	99	87	11.1	0.8	0.4
197	64	M	2	8	0	1.58	62	2	B	37	28.21	NO	NO	NO	33	1.4	54	127	11.8	0.7	0.5
198	66	M	2	13	1	0.69	44	3	D	88	24.61	NO	NO	NO	37	1.3	57	122	13.4	0.8	0.4
199	57	M	2	16	0	2.12	72	2	B	18	18.3	NO	NO	NO	29	1.2	65	99	14.6	0.3	0.2
200	48	M	2	8	0	1.63	44	3	B	54	20.31	NO	NO	NO	18	1.1	87	105	15.8	0.7	0.3
201	66	M	3	9	0	1.63	48	3	B	93	20.76	NO	YES	NO	53	2	35	85	12.9	1.2	0.7
202	52	F	2	16	1	0.88	39	3	D	93	23.29	NO	NO	NO	21	0.7	97	114	11.1	0.8	0.5
203	55	M	3	18	1	1.87	54	2	D	37	18.21	NO	NO	NO	34	0.9	99	154	17.1	0.3	0.3
204	49	M	2	12	1	1.79	51	2	D	43	23.24	NO	NO	NO	23	0.8	107	92	11.4	0.8	0.2
205	63	M	3	8	0	0.83	39	3	B	18	21.32	NO	NO	NO	34	0.8	97	112	11.8	0.7	0.3
206	65	M	3	9	0	1.51	48	3	B	32	23.76	NO	NO	NO	23	1.4	53	104	13.6	1.6	0.8
207	65	M	3	10	0	0.61	38	3	B	84	16.71	NO	NO	NO	29	0.9	92	84	12.5	0.7	0.1
208	52	M	2	6	0	1.31	47	3	B	0	21.32	NO	YES	NO	19	0.8	103	81	12.4	0.8	0.3
209	63	F	3	8	0	0.85	38	3	B	0	23.67	NO	NO	NO	26	0.5	99	102	14.3	0.8	0.4
210	66	M	2	9	1	1.23	61	2	D	0	29.53	NO	YES	NO	25	0.9	90	133	15.1	0.8	0.6
211	54	F	2	7	0	0.76	58	2	B	0	20.32	YES	NO	NO	25	0.7	102	87	11.3	0.8	0.4
212	60	M	3	16	0	0.97	46	3	B	0	29.11	NO	NO	NO	24	0.6	105	83	15.3	1.3	1

213	53	M	2	12	0	0.65	27	4	B	65	19.04	YES	NO	NO	27	0.8	108	187	14.5	0.5	0.3
214	54	M	2	10	0	1.62	38	3	B	35	20.76	YES	YES	NO	26	1.2	67	227	14.9	0.5	0.2
215	64	F	3	9	0	0.83	47	3	B	0	25.21	NO	NO	NO	25	0.8	69	114	11.3	0.9	0.4
216	75	M	3	11	1	0.63	41	3	D	55	16.12	NO	NO	NO	32	0.8	83	184	12.1	0.4	0.2
217	60	F	2	13	0	0.53	27	4	B	0	18.12	NO	NO	NO	27	0.7	98	85	10.8	0.6	0.4
218	61	M	2	6	0	1.73	65	2	B	41	29.82	NO	NO	NO	35	1.4	52	142	12.3	0.8	0.6
219	65	M	2	9	1	0.64	44	3	D	84	23.21	NO	NO	NO	35	1.3	56	122	12.6	0.7	0.4
220	57	M	2	10	0	1.98	68	2	B	21	19.32	NO	NO	NO	28	1.2	67	83	13.9	0.3	0.2
221	48	M	2	14	0	1.81	48	3	B	54	21.21	NO	NO	NO	18	1	89	112	15.6	0.6	0.3
222	65	M	3	19	0	1.54	45	3	B	87	20.76	NO	YES	NO	53	1.9	35	93	12.7	1.1	0.7
223	53	F	2	18	1	0.95	38	3	D	93	22.45	NO	NO	NO	21	0.8	95	155	13.4	0.6	0.5
224	55	M	3	12	1	1.87	54	2	D	33	18.54	NO	NO	NO	35	0.7	103	156	16.9	0.4	0.3
225	47	M	2	10	1	1.79	56	2	D	44	23.24	NO	NO	NO	20	0.9	105	91	11.8	0.5	0.3
226	62	F	2	8	0	1.13	59	2	B	0	28.59	NO	NO	NO	25	0.7	97	152	13.4	0.8	0.5
227	43	M	3	6	0	1.14	53	2	B	33	26.19	NO	NO	NO	31	0.8	114	95	12.7	0.4	0.2
228	62	M	1	9	0	65	28	4	A	15	21.91	NO	NO	NO	41	1.4	55	86	11.9	0.4	0.3
229	61	M	2	10	0	1.31	45	3	B	23	18.54	NO	NO	NO	32	1.2	66	98	13.6	0.5	0.2
230	70	M	3	9	0	1.29	32	3	B	8	19.85	NO	NO	NO	18	0.8	88	93	12.9	0.5	0.3
231	62	M	3	10	1	0.75	25	4	D	17	21.48	YES	YES	NO	25	0.8	97	90	12.7	0.8	0.5
232	61	M	2	9	1	0.63	27	4	D	65	17.12	NO	NO	NO	32	1.7	42	162	11.6	0.8	0.5
233	60	M	2	8	0	1.48	65	2	B	63	19.62	NO	NO	NO	21	1.1	80	95	14.6	0.6	0.4
234	46	M	3	6	0	1.72	64	2	B	0	25.65	NO	NO	NO	15	1.1	81	158	12.3	1.2	0.6
235	64	M	2	9	0	2.12	58	2	B	37	21.27	NO	NO	NO	22	0.8	93	135	11.9	0.4	0.2
236	67	M	2	8	1	1.43	57	2	D	23	26.98	NO	NO	NO	19	1.1	68	53	14.1	0.5	0.4
237	58	M	2	8	0	2.22	73	2	B	39	16.94	NO	NO	NO	17	1.2	67	75	14.4	0.6	0.3
238	61	M	2	10	0	1.23	58	2	B	44	19.38	YES	NO	NO	15	1.1	74	112	13.6	0.4	0.2
239	62	M	2	9	1	0.85	35	3	D	17	21.85	NO	NO	NO	18	1	82	78	13.1	0.9	0.5
240	63	M	2	7	0	1.77	71	2	B	39	23.59	NO	NO	YES	20	1.2	65	77	12.6	0.7	0.4
241	68	M	2	6	0	1.12	47	3	B	8	24.65	YES	NO	NO	27	1.2	62	168	11.2	0.7	0.4
242	58	M	2	8	0	1.58	69	2	B	47	26.25	NO	NO	YES	19	1.2	65	103	12.8	0.3	0.1
245	72	M	2	9	0	0.76	47	3	B	47	18.66	NO	NO	NO	16	0.8	88	154	13.7	0.5	0.2
246	58	M	1	8	0	1.32	42	3	A	0	15.87	NO	NO	NO	21	0.9	95	114	13.9	0.7	0.3
247	54	M	1	6	0	1.92	74	2	A	17	18.54	NO	NO	NO	22	0.7	103	88	13.3	0.5	0.3
248	63	M	1	7	0	1.25	55	2	A	54	20.57	NO	NO	NO	19	0.8	98	174	13.9	0.6	0.3
249	63	M	2	9	0	1.31	75	2	B	81	21.36	NO	NO	NO	31	0.5	115	137	12.6	0.6	0.3
250	48	F	2	12	0	1.48	44	3	B	0	21.38	YES	YES	NO	19	0.7	103	133	13.1	0.6	0.2
251	70	M	2	10	0	1.72	67	2	B	0	22.83	NO	NO	NO	38	1	75	124	13.8	0.7	0.5
252	62	M	3	10	0	1.94	71	2	B	0	31.39	NO	NO	YES	22	1.2	64	158	13.8	0.5	0.3
253	74	M	2	14	1	1.48	48	3	D	55	18.82	NO	NO	NO	19	1.2	58	136	12.3	0.3	0.2
254	60	M	2	9	0	1.24	47	3	B	12	22.96	NO	NO	NO	27	1.4	55	108	15.1	0.7	0.4
255	68	M	2	6	0	1.71	81	1	B	52	23.43	NO	NO	YES	32	1.3	56	97	14.4	0.3	0.2
256	61	M	1	9	0	1.84	66	2	A	15	22.79	NO	NO	NO	17	0.6	116	98	13.9	0.4	0.3
257	63	M	2	10	0	0.85	42	3	B	78	17.28	NO	NO	NO	21	0.8	101	130	12.8	0.8	0.3
258	75	M	2	8	0	1.54	64	2	B	0	24.38	NO	NO	NO	19	1.2	57	90	13.4	1.2	0.7
259	63	F	2	6	0	0.75	38	3	B	0	22.79	NO	NO	NO	27	1.2	65	89	12.2	0.8	0.5
260	54	M	3	7	0	1.31	46	3	B	37	23.58	NO	NO	NO	19	1.2	68	77	12.9	0.6	0.3
261	56	M	2	9	0	0.52	28	4	B	45	18.51	NO	NO	NO	21	0.7	111	154	14.1	0.6	0.3
262	64	M	2	8	0	0.76	26	4	B	14	28.75	NO	NO	NO	26	0.6	113	123	11.8	0.4	0.3
263	62	M	2	12	0	1.12	46	3	B	47	23.54	NO	NO	NO	34	1.3	58	74	15.2	1.1	0.6
264	72	M	2	18	0	0.94	39	3	B	53	15.62	NO	NO	NO	23	0.7	101	104	12.8	0.3	0.1
265	60	M	2	11	0	1.24	64	2	B	19	18.75	NO	NO	NO	55	1.4	55	74	13.6	0.5	0.3
264	68	F	2	8	0	0.76	36	3	B	0	29.64	NO	NO	NO	32	0.8	67	115	12.2	0.4	0.2
265	58	F	2	6	0	0.68	38	3	B	0	21.34	NO	NO	NO	38	0.8	82	90	12.1	0.7	0.4
266	67	M	3	10	0	1.47	48	3	B	31	24.41	NO	NO	NO	23	1.3	53	106	13.4	1.8	0.9

267	63	M	1	8	0	1.11	53	2	A	55	20.57	NO	NO	NO	19	0.6	101	172	13.6	0.6	0.4
268	65	M	3	14	1	0.84	36	3	D	17	27.34	NO	NO	NO	26	1	77	154	14.2	0.5	0.3
269	46	M	2	11	0	3.12	78	2	B	25	22.49	YES	YES	NO	19	1	89	215	15.2	0.6	0.3
270	58	M	1	6	0	2.23	82	1	A	0	26.47	NO	NO	NO	27	1.2	67	117	12.4	0.5	0.3
271	70	M	3	7	0	0.89	43	3	B	46	19.65	NO	NO	NO	21	1	77	89	12.8	0.5	0.1
272	58	M	2	6	0	0.88	28	4	B	63	26.34	NO	NO	NO	29	0.7	103	148	12.7	0.6	0.4
273	45	M	2	8	0	1.12	32	3	B	8	15.21	NO	NO	NO	27	0.8	113	77	11	0.6	0.3
274	63	M	3	10	0	1.58	63	2	B	37	29.82	NO	NO	NO	36	1.3	56	132	11.8	0.7	0.6
275	66	M	2	16	1	0.57	47	3	D	84	24.61	NO	NO	NO	37	1.3	56	138	12.6	0.7	0.4
276	63	M	1	8	0	0.64	28	4	A	19	21.91	NO	NO	NO	41	1.4	55	89	12.7	0.5	0.3
277	64	M	2	6	0	1.34	46	3	B	22	17.77	NO	NO	NO	33	1.2	65	97	13.8	0.4	0.3
278	53	M	2	7	0	1.38	62	2	B	0	21.47	NO	YES	NO	34	1.5	54	102	13.6	1.2	0.7
279	62	M	3	14	1	0.55	24	4	D	0	25.86	NO	NO	NO	40	1.1	72	151	12.8	0.5	0.3
280	71	M	3	9	0	0.94	41	3	B	0	21.56	NO	YES	NO	25	0.7	101	88	13.4	0.5	0.3
281	54	M	2	12	0	0.86	44	3	B	22	22.42	NO	NO	NO	28	0.9	103	95	11.6	0.6	0.3
282	76	M	2	10	1	1.51	48	3	D	53	18.12	NO	NO	NO	22	1.2	58	163	12.3	0.5	0.2
283	62	M	2	9	0	1.14	46	3	B	9	23.43	NO	NO	NO	27	1.3	55	113	14.6	0.6	0.4
284	65	F	2	6	0	1.44	46	3	B	0	22.46	YES	YES	NO	36	1.1	53	127	12.6	0.5	0.2
285	57	M	1	7	0	0.88	32	3	B	92	17.44	NO	NO	NO	23	0.6	114	87	9.9	0.7	0.4
286	66	F	2	11	0	1.49	47	3	B	0	21.96	YES	NO	NO	35	1.1	51	178	12.4	0.3	0.2
287	71	M	3	7	0	0.88	38	3	B	0	20.94	NO	NO	NO	32	1.1	75	112	12.8	0.7	0.4
288	62	M	1	6	0	1.34	56	2	A	51	20.57	NO	NO	NO	18	0.8	102	182	13.4	0.6	0.4
289	66	M	3	16	1	0.72	33	3	D	18	27.34	NO	NO	NO	24	1	79	152	14.2	0.5	0.3
290	45	M	2	9	0	3.39	83	1	B	23	22.49	YES	YES	NO	18	1	90	222	15.7	0.7	0.3
291	58	M	1	7	0	2.24	78	2	A	0	27.17	NO	NO	NO	25	1.2	65	129	12.9	0.6	0.3
292	72	M	3	6	0	0.96	44	3	B	47	19.65	NO	NO	NO	21	1	77	96	12.9	0.5	0.1
293	57	M	2	12	0	0.89	27	4	B	63	26.34	NO	NO	NO	31	0.8	101	147	12.4	0.6	0.4
294	44	M	2	14	0	0.96	31	3	B	9	14.03	NO	NO	NO	28	0.7	115	72	11	0.5	0.3
295	64	M	3	16	0	1.54	66	2	B	37	29.82	NO	NO	NO	36	1.4	55	134	11.8	0.7	0.6
296	67	M	2	20	1	0.64	44	3	D	83	24.61	NO	NO	NO	36	1.3	57	138	12.6	0.7	0.4
297	62	M	1	8	0	0.55	23	4	A	19	21.91	NO	NO	NO	38	1.4	55	94	11.8	0.5	90
298	63	M	2	6	0	1.33	45	3	B	20	17.77	NO	NO	NO	33	1.2	64	103	13.6	0.4	0.3
299	54	M	2	7	0	1.64	54	2	B	0	21.34	NO	YES	NO	34	1.5	54	90	13.8	1.3	0.8
300	61	M	3	9	1	0.64	25	4	D	0	27.91	NO	NO	NO	40	1.1	74	151	12.1	0.5	0.3
301	72	M	3	16	0	0.82	42	3	B	0	21.37	NO	YES	NO	25	0.7	101	87	13.1	0.5	0.3
302	53	M	2	12	0	0.88	42	3	B	22	21.32	NO	NO	NO	27	0.8	103	94	11.1	0.6	0.3
303	75	M	2	14	1	1.48	48	3	D	53	17.57	NO	NO	NO	22	1.2	58	163	12.3	0.5	0.2
304	63	M	2	8	0	1.12	45	3	B	10	23.43	NO	NO	NO	29	1.4	53	112	14.9	0.7	0.4
305	65	F	2	6	0	1.54	48	3	B	0	22.67	YES	YES	NO	36	1.2	54	188	12.7	0.5	0.1
306	57	M	1	7	0	0.94	33	3	B	94	17.44	NO	NO	NO	23	0.6	115	82	9.6	0.7	0.4
307	67	F	2	9	0	1.53	48	3	B	0	22.67	YES	NO	NO	35	1.2	53	174	11.9	0.3	0.2
308	72	M	3	12	0	0.85	37	3	B	0	22.84	NO	NO	NO	32	1.1	75	115	12.6	0.7	0.4
309	60	M	2	14	0	1.68	64	2	B	41	28.97	NO	NO	NO	35	1.4	53	142	12.3	0.8	0.6
310	64	M	2	18	1	0.84	46	3	D	82	23.21	NO	NO	NO	35	1.3	56	145	13.3	0.7	0.4
311	54	M	2	10	0	0.87	42	3	B	24	21.64	NO	NO	NO	27	0.8	101	94	10.8	0.7	0.3
312	52	M	2	9	0	1.24	59	2	B	0	23.98	NO	YES	NO	32	1.5	53	98	13.4	1.3	0.8
313	62	M	3	8	1	0.95	42	3	D	0	25.65	NO	NO	NO	34	1.1	72	141	12.7	0.5	0.3
314	58	F	2	7	0	0.57	35	3	B	0	22.38	NO	NO	NO	37	0.8	81	90	11.9	0.7	0.4
315	65	M	3	16	0	1.49	47	3	B	30	23.43	NO	NO	NO	22	1.4	52	104	13.4	1.8	0.9
316	66	M	3	14	0	0.61	33	3	B	82	15.49	NO	NO	NO	26	0.8	93	73	11.2	0.6	0.1
317	53	M	2	12	0	0.95	42	3	B	0	20.88	NO	YES	NO	20	0.8	102	81	12.7	0.8	0.3
318	70	F	3	14	0	0.49	34	3	B	0	24.15	NO	NO	NO	25	0.5	98	102	14.7	0.8	0.5
319	65	M	2	9	1	1.17	60	2	D	0	29.76	NO	YES	NO	24	0.9	89	121	15.1	0.7	0.6
320	55	F	2	7	0	0.74	58	2	B	0	20.14	YES	NO	NO	28	0.7	102	90	10.8	0.7	0.4

321	60	M	3	18	0	0.85	42	3	B	0	28.11	NO	NO	NO	27	0.8	101	77	15.3	1.3	1
322	52	M	2	6	0	0.64	27	4	B	61	19.48	YES	NO	NO	29	0.7	109	124	16.3	0.5	0.4
323	54	M	2	8	0	1.53	34	3	B	33	20.76	YES	YES	NO	26	1.2	68	225	14.4	0.4	0.2
324	66	F	3	10	0	0.94	46	3	B	0	23.94	NO	NO	NO	24	0.9	67	104	10.6	0.9	0.6
325	77	M	3	14	1	0.54	36	3	D	52	15.26	NO	NO	NO	31	0.9	83	164	11.4	0.2	0.1
326	62	F	2	6	0	0.62	28	4	B	0	18.45	NO	NO	NO	28	0.6	99	98	10.8	0.7	0.4
327	64	M	2	8	0	1.55	61	2	B	36	29.82	NO	NO	NO	34	1.3	55	146	11.8	0.7	0.6
328	67	M	2	7	1	0.96	48	3	D	85	24.61	NO	NO	NO	36	1.3	56	132	12.8	0.8	0.4
329	57	M	2	12	0	2.14	69	2	B	19	18.34	NO	NO	NO	28	1.2	65	97	14.6	0.3	0.2
330	48	M	2	8	0	1.76	48	3	B	51	20.31	NO	NO	NO	18	1	89	114	15.8	0.7	0.3
331	66	M	3	9	0	1.58	45	3	B	85	20.76	NO	YES	NO	54	2	35	85	12.4	1.2	0.7
332	53	F	2	6	1	0.82	37	3	D	91	23.29	NO	NO	NO	22	0.6	98	117	11.8	0.6	0.5
333	54	M	3	12	1	1.97	55	2	D	35	17.54	NO	NO	NO	33	0.7	102	132	17.3	0.5	0.3
334	47	M	2	7	1	1.98	56	2	D	44	23.24	NO	NO	NO	22	0.9	105	91	11	0.5	0.2
335	63	M	3	10	0	1.14	46	3	B	14	21.32	NO	NO	NO	33	0.7	95	122	11.8	0.6	0.3
336	65	M	1	8	0	1.64	63	2	A	61	23.12	NO	NO	NO	35	0.5	122	145	11.7	0.3	0.2
337	54	M	3	6	1	1.52	58	2	D	71	20.24	NO	NO	NO	31	0.8	110	148	11.8	0.5	0.4
338	54	M	2	12	0	0.46	25	4	B	32	19.75	NO	YES	NO	22	0.6	114	148	12.8	0.5	0.3
339	52	M	2	10	0	1.57	78	2	B	79	27.84	YES	NO	NO	21	0.7	114	167	11.9	0.5	0.4
340	82	M	3	17	0	0.58	44	3	B	19	27.08	YES	YES	NO	38	1.2	55	112	12.2	0.6	0.4
341	71	M	2	9	0	1.34	68	2	B	0	22.87	YES	YES	NO	23	1.1	74	189	11.6	0.4	0.3
342	62	M	2	7	0	2.08	78	2	B	44	18.47	NO	NO	NO	31	1	80	169	10.6	0.8	0.5
343	70	M	2	8	0	0.85	36	3	B	0	21.27	NO	NO	NO	33	1	76	105	12.2	0.8	0.4
344	72	M	2	6	0	0.83	44	3	B	47	17.56	NO	NO	NO	35	0.9	85	168	11.2	0.5	0.3
345	66	F	2	12	0	1.36	44	3	B	0	22.67	YES	YES	NO	34	1.1	54	116	12.3	0.3	0.1
346	59	M	1	8	0	0.63	28	4	B	91	17.44	NO	NO	NO	23	0.5	119	82	9.6	0.7	0.4
347	72	M	3	6	0	0.86	42	3	B	0	21.37	NO	YES	NO	22	0.7	100	94	11.8	0.5	0.3
348	54	M	2	7	0	0.94	42	3	B	24	20.88	NO	NO	NO	24	0.9	102	94	11.2	0.6	0.3
349	50	M	2	9	0	1.21	57	2	B	0	22.64	NO	YES	NO	32	1.5	54	91	13.8	1.3	0.8
350	64	M	3	12	1	0.54	24	4	D	0	28.64	NO	NO	NO	36	1.1	71	145	12.6	0.5	0.3
351	63	F	2	10	0	1.73	62	2	B	0	27.21	NO	YES	NO	30	0.7	92	178	14.8	0.8	0.4
352	68	F	2	9	0	0.74	36	3	B	0	22.08	NO	NO	NO	32	0.7	90	72	11.1	0.5	0.3
352	54	M	3	10	0	1.42	44	3	B	35	20.14	NO	NO	NO	21	1.2	68	90	15.3	0.8	0.5
354	67	M	2	12	0	1.29	59	2	B	63	21.64	NO	NO	NO	38	1.5	47	138	13	0.6	0.3
355	61	F	2	9	0	1.12	59	2	B	0	28.72	NO	NO	NO	28	0.6	98	164	13.4	0.7	0.5
356	42	M	3	8	0	1.64	54	2	B	34	24.86	NO	NO	NO	28	0.6	117	96	12.5	0.6	0.3
357	58	M	1	6	0	0.59	23	4	A	15	21.91	NO	NO	NO	41	1.4	55	82	12.1	0.4	0.2
358	61	M	2	6	0	1.27	43	3	B	22	17.77	NO	NO	NO	31	1.2	65	100	13.6	0.4	0.2
359	70	M	3	7	0	1.38	32	3	B	7	18.17	NO	NO	NO	17	0.9	86	88	13.3	0.5	0.2
360	61	M	3	10	1	0.71	23	4	D	19	21.48	YES	YES	NO	22	0.8	96	91	12.8	0.8	0.6
361	60	M	2	18	1	0.66	28	4	D	68	16.33	NO	NO	NO	34	1.8	40	177	11.6	0.9	0.5
362	62	M	2	6	0	1.52	66	2	B	62	19.62	NO	NO	NO	18	1	80	85	14.3	0.7	0.4
363	48	M	3	8	0	1.78	65	2	B	0	27.34	NO	NO	NO	17	1.1	81	216	12.7	1.2	0.6
364	66	M	2	6	0	2.12	72	2	B	38	22.28	NO	NO	NO	23	0.9	92	146	13.6	0.5	0.2